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Ontario

ROYAL COMMISSION OF INQUIRY INTO CERTAIN
DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND
RELATED MATTERS.

Hearing held
8th floor
180 Dundas Street West
Toronto, Ontario

The Honourable Mr. Justice S.G.M. Grange

Commissioner

P.S.A. Lamek, Q.C.

Counsel

E.A. Cronk

Associate Counsel

Thomas Millar

Administrator

MacLEOD

Transcript of evidence
for

November 9, 1983

VOLUME 63

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63

BAIN (cont'd)

X: Shueh

Re: Roland

P&H

In dr. P&H



ROYAL COMMISSION OF INQUIRY INTO CERTAIN
DEATHS AT THE HOSPITAL FOR SICK CHILDREN
AND RELATED MATTERS.

Hearing held on the 8th Floor,
180 Dundas Street West, Toronto,
Ontario, on Wednesday, the 9th
day of November, 1983.

- - - - -

THE HONOURABLE MR. JUSTICE S.G.M. GRANGE - Commissioner
THOMAS MILLAR - Administrator
MURRAY R. ELLIOT - Registrar

- - - - -

APPEARANCES:

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D. HUNT)	Counsel for the Attorney
L. CECCHETTO)	General and Solicitor General
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M. O'CONNOR)	Nurses' Association of Ontario
	and 35 Registered Nurses at
	The Hospital for Sick Children

(Cont'd)



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E. FORSTER	Counsel for Phyllis Trayner - Nurse
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S. LABOW	Counsel for Mr. & Mrs. Gosselin, Mr. & Mrs. Gionas, Mr. & Mrs. Inwood, Mr. & Mrs. Turner, and Mr. & Mrs. Lutes (parents of deceased children)
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J. SHINEHOFT	Counsel for Lorie Pacsai and Kevin Garnet (parents of deceased child Kevin Pacsai)



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---Upon commencing at 10:15 a.m.

MR. SHINEHOFT: Good morning,
Mr. Commissioner.

THE COMMISSIONER: Yes, Mr. Shinehoft.

DR. HARRY WILLIAM BAIN, Resumed

CROSS-EXAMINATION BY MR. SHINEHOFT: (Continued)

Q. Dr. Bain, good morning.

A. Good morning, Mr. Shinehoft.

Q. If I could recapitulate
the evidence at the latter part of yesterday we were
talking about the pathology of transient adrenal
insufficiency and I believe you indicated, Doctor,
that you could not comment or were unaware of any
pathological findings on autopsy of transient
adrenal insufficiency.

A. Well, I think the point was -
I haven't got my breath yet from walking down, so
bear with me if I stumble here a bit.

Q. Okay.

A. I think the point I was trying
to make is that I know of no pathology in transient
adrenal insufficiency because, as I say, the cases
have been few and far between, there have been
clinical diagnoses usually if the patient has died
and then they have tried to say something else.



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3 However, that doesn't bother me because as
4 Dr. Spielberg testified, he used the word patho-
5 physiology which may in fact describe what a transient
6 adrenal insufficiency is and, therefore, it will be
7 an enzyme defect and therefore one would not expect
8 if someone died of it that there would be any
9 pathology.

10 Q. I see. Well, I asked you
11 yesterday, Doctor, at Volume No. 62, page 4023, line
12 8:

13 "Q. If I were to say to you,
14 Doctor, that there are some endo-
15 crinologists that are of the opinion
16 that the condition of transient adrenal
17 insufficiency will leave an abnormality
18 of the adrenal glands either in size
19 or in architecture, would you agree or
20 disagree with that?"

21 And your answer was:

22 "A. I cannot agree and I cannot
23 disagree..."

24 A. Correct, because they may be
25 either. I think that is what they are saying,
there may be an enzyme defect and it won't show.
There may be a structural thing because there have



1
2 been cases of patients with a syndrome very similar
3 to this who have eventually died some years later
4 and had some structural changes; many years later.

5 Q. So, you are prepared to
6 concede, Doctor, that there are some people with
7 this condition who died who have some abnormalities
8 of the adrenal glands either in size or in architec-
9 ture?

10 A. That is an impossible question
11 to answer, Mr. Shinehoft, because, as I say, usually
12 these patients do not die. There are a couple of
13 cases in the literature where they have put this
14 diagnosis on at one time; one in particular that is
15 in French and I mentioned yesterday and I have to
16 have it translated because I don't understand it
17 clearly myself but I will see that you people get it.
18 But they may in later life have that, yes.

19 If a patient on the other hand had
20 what was considered clinically, and that's what I'm
21 basing my diagnosis on is the clinical facts which
22 I will be glad to reiterate, if they are based on
23 the clinical things and the patient lives you don't
24 have the opportunity, you don't have - except later
25 on one could possibly test it out with the appropriate
endocrin tests over the next week or so.



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3 If the patient does that at that time
4 there may be changes, in which case it probably wasn't
5 going to be transient, that was your diagnosis but
6 it was probably going to be fixed, whereas, it might
7 be an enzyme thing which would not show on autopsy.

8 Q. Yes, I am appreciative of the
9 enzyme thing.

10 A. Yes, okay.

11 Q. Would you go so far as to
12 acknowledge, Doctor, that there are some endocrinolo-
13 gists who believe that the condition of transient
14 adrenal insufficiency may leave pathological symptoms
15 on autopsy?

16 A. I have not seen that written
17 but if you say it to me and you have it written
18 somewhere I am sure there would be some endocrinolo-
19 gists who would say that but they should have put
20 a case report somewhere, that's all.

21 Q. I see. Now, could you refer,
22 Doctor, to Exhibit 106C which you looked at yesterday
23 and which is the post mortem, the autopsy at post
24 mortem. I think it is B, 106B.

25 A. Yes.

Q. And if I could ask you to
review with me the - it looks like page 3 of that



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report, Section F. Have you found that, Doctor?

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A. Yes, I have that, thank you.

4

Q. And that is the Genital

5

Urinary System?

6

A. Yes.

7

Q. Could you indicate to the

8

Commissioner what it says about the adrenals, please.

9

A. Well, it says that the right

10

one is 3.1 grams, the left was 3.4 grams and that

11

they were grossly normal. That means when you looked

12

at them in the gross, just sort of they looked

13

normal.

Q. Could you comment, or would

14

you care to comment about their weight?

15

A. That weight, I would have to

16

go back to my books. Certainly it is within the

17

normal range and maybe on the higher side but as

18

you will recall the weights in this particular age

19

group are very variable and I don't think anyone

20

could pick a specific case and say what they should

21

weigh because in utero they are going to weigh -

22

I haven't got my exact figures on weights I have it

23

written down somewhere. They would weigh double or

24

triple or even more of that.

Q. But you are not disagreeing

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with the pathologist who says that the adrenals were
grossly normal?

4

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A. No, grossly normal is the same
as if you looked at something lying on the floor
there that looked a piece of meat and adrenal and
said looked grossly normal.

8

Q. I'm aware of that.

9

A. Yes. I'm not disagreeing, nor
with his scales, no.

10

11

THE COMMISSIONER: Normal I take it
has nothing to do with the weight?

12

THE WITNESS: No.

13

THE COMMISSIONER: It is appearance.

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THE WITNESS: It is appearances,
yes; that is, there were no obvious TB or things
which is one of the things that we are concerned
about or that there weren't very little tiny things
that hadn't been there or atrophy or hemorrhage into
them that sometimes happens in babies, that sort of
thing.

20

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22

MR. SHINEHOFT: Q. And is it normal
to do a microscopic examination of the adrenals on
an autopsy?

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A. It is normal to do microscopic
examinations on everything on autopsy, yes.



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Q. And would it be fair to say that there would be a comment if there was some abnormality of the adrenals on microscopic examination if in fact there were?

A. I think that if you read my report you will see that I went back to the pathologist and asked for that information and he did not find anything abnormal microscopically. That is in my report.

Q. Okay. So, the adrenals are normal on gross autopsy, normal in weight and normal on microscopic examination.

A. As normal as one can judge on the basis of cells, that is, he said there was no evidence when I phoned him of Addison's Disease, that is the atrophy and we know that because, well, they wouldn't be that large if they had been born. That is a tough one.

Q. But you do comment in your evidence and I was going to get into that later on about children with Addison's Disease and you refer to it at page 3451, line 7 and you refer to it in several other places, Doctor. Could you tell me why you do refer to children with Addison's Disease when you excluded that diagnosis for Kevin Pacsai?



1
2 A. Because I think probably, I
3 don't know the context, I think we were probably
4 talking about the common and uncommon things that
5 occur in this age group and I probably said that
6 the adrenal genital syndrome was one of the things
7 that is common in this age group and it is a little
8 different in that it has an overaction in part of
9 the gland, a relatively normal action of another
10 and an underaction of the part that we are concerned
11 about. It has a different pathological structure.

12 In Addison's Disease with all three
13 parts which fit this better from a diagnosis because
14 the blood sugar was down earlier on, one tends to
15 get atrophy. On the other hand, when one gets into
16 enzyme defects then, as I say, those are things that
17 are not going to show in the structural changes.

18 Q. That's right. But I refer
19 you to one comment that you made. You said that:

20 "With those electrolyte pictures and
21 a blood sugar too because true
22 Addison's Disease that is the other, --
23 we don't see it, it is awfully rare..."

24 A. Yes. Well, those two state-
25 ments don't go together, so, obviously I said
something wrong there when I said we don't see it



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and that it is rare because if it is rare we still
see it.

3

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Q. I see.

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A. I have seen two only in my life-
time, yes.

6

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Q. And you are aware that
Dr. Rowe has come here and he has given his evidence.
His evidence is that until you prepared your report
he had never heard of this condition. Are you aware
of that?

10

11

A. No, I have not heard him say
that.

12

13

Q. I can give you the references
if you wish.

14

15

Dr. Fowler gave that same evidence.

16

A. That's fine.

17

Q. Dr. Becker gave that same
evidence.

18

19

A. Well, I can't really believe
that they had never heard of it because they all
trained at Sick Children's. It is one of the things
that we would be talking about, but that is all right,
they may have been referring to as applied here until
they say my report. But as far as not knowing of
the conditions, I would be very surprised.

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Q. Would you comment about
Dr. Cutz who also made a similar comment?

A. I guess I have to hear those
statements because Dr. Cutz who did the pathology
would be seeing patients with all of those types of
adrenal insufficiency whether due to Addison's
Disease because the pathologists ---

THE COMMISSIONER: There might have
been, I can't remember the instance but it could have
been the transient.

THE WITNESS: Yes.

THE COMMISSIONER: Of course the
pathologist would know nothing about transient.

THE WITNESS: That's right, if that
is what they are saying, that's fine, if we are
talking about transient.

MR. SHINEHOFT: Q. I'm not talking
about adrenal insufficiency, Doctor.

A. Oh.

Q. I think that is a well
recognized syndrome. I'm talking about transient
adrenal insufficiency.

A. Well, adrenal insufficiency
and whether it is transient or otherwise is adrenal
insufficiency and then there are many causes, one



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of which has been alluded to by many people as
transient because they have it biochemically and
it goes away and they get better if they don't die
of it in the attack.



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Q I am prepared to give you the references.

A But four doctors don't think that.

Q And until you prepared your report they had really never heard of the condition of transient adrenal insufficiency?

A Well, as I say, it is in every standard textbook, including Nelson's textbook on Paediatrics, and they may have meant that they had not seen such a thing. But remember that some people when they get into subspecialties they know a tremendous amount about that, a great deal more than I would do, and you can't know everything about everything in medicine.

Q I understand, Doctor.

A Thank you.

Q If I could ask you about another comment that you made at page 3450, line 17, you are talking about digoxin and you said, and I will use your exact words:

"So it would seem that his level around the 10 mark which I would not say is not dangerous but nevertheless we have certainly seen people not upset with it."



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A. Yes.

Q. I am surprised; Doctor, at that comment to be honest with you.

A. Well ---

Q. What in your opinion is the therapeutic dosage of digoxin?

A. Well, I think therapeutic levels that people try to attain are somewhere under 2 and 3, sort of thing. I thought Dr. Spielberg testified here, and maybe he did not. But, not too long ago we had a patient who took granny's pills and a big dose and with levels of 14, I think the level was, was sitting there laughing and absolutely no symptoms whatsoever. Everybody in medicine has had that experience.

We have also seen children who are on therapeutic doses who have had higher levels, and I won't say how high because you can ask the clinical pharmacologist that. I can just speak of the cases I have heard of recently.

Q. In a comparative way, Doctor, you are talking about five times the amount of the upper range of the therapeutic level?

A. Not of the upper range, no, because most people will accept up to about 3-1/2, so



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if you want to say 3, that is fine.

3

Q. Okay, three times the ---

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A. Well, it is a variable, but that

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is fine, you go ahead, that doesn't bother me, that
statement.

6

Q. Would it be fair to say that it

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is in the toxic range that level of 10?

8

A. It certainly is supposed to be

9

in the toxic range, but there are some children with

10

it who do not show toxic signs, that is the point I

11

was trying to make.

12

Q. I see.

13

A. It is not necessarily fatal I

14

think is the point I was trying to make.

15

Q. But it is something you would be

16

concerned about?

A. You bet your life, yes.

17

Q. And it is something that is

18

somewhat abnormal to have babies with ante mortem

19

levels of 10, or greater than 10, it is not common?

20

A. It is scary, yes.

21

Q. It is rare, in your experience,

is it not?

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A. I don't have any experience in

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that, well, maybe way a long time ago I did. As I say,

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the cardiologists took over. Yes, I know of them, but actual patients that I look after, I run a consulting practice, Mr. Shinehoft, and when you do a consulting practice maybe it is the refuge of the destitute or whatever. Usually you see the patient once or twice and the patient goes home and someone else carries on the day-to-day care.

Q. But you are of the view, Doctor, that this baby was in very poor condition at St. Joseph's Hospital; he had very high potassium levels; he was then sent to McMaster. He was started on an IV and it would appear they controlled his potassium?

A. I wonder if I could just go back a bit, because I think it is important that you understand what I understand about the baby.

When the baby came to St. Joseph's, and I am talking off the top of my head now and so I may make the odd error, but you can correct me if I do. When the baby came to St. Joseph's Hospital he was awfully sick. He was mottled; he was shocked; he had no obtainable blood pressure at all. Now, there was a little difference there that I had a little trouble understanding, because it seemed that after he was there the best part of an hour he got even worse and they pushed the panic button. Because at



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that time they even had to ventilate him, they had to put a tube down I guess and bag him, because then his respirations were failing. They had done some electrolytes and they showed that his kidneys were not working well, the BUN which is normally the upper level of 20 was 31 or 34, as I recall, 31 I think it was, so the kidneys were not working well. The sodium and the chloride were down, and the potassium as you recall was high. There were a few other things involving his liver too, some other blood clotting tests as well.

12

Q. The liver had enlarged a bit,

13

had it not?

14

A. They mentioned, their evidence

15

that the baby was in heart failure was that the liver was down 3 centimetres, when the heart fails it backs up and that is sometimes the only way in ---

17

Q. That is the right costal margin,

18

is it?

19

A. Yes. The interesting thing was

20

when he came to Sick Children's it was still 3

21

centimetres and he wasn't supposed to be in failure so I don't really know what the evidence of failure was at that time.

22

23

Q. You have given evidence, and I

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25



B.6

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don't want to belabour the point, this baby was in
pretty bad shape ---

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A. Could I just finish?

5

Q. Yes.

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A. I am sorry. In any case they

7

jumped on the baby at that time, 45 minutes or an
hour after the baby arrived because he was pretty

8

desperate then and they bagged him, put a tube down
and bagged him and gave some intravenous, gave some

9

10

intravenous albumin and several drugs I think, and

11

some digoxin, because they felt he may be in failure.

12

They felt that his diagnosis was overwhelming

13

infection, that was No. 1; and the second one a little
later was paroxysmal tachycardia, a really fast heart.

14

I don't think they thought of that right off because

15

the rate was only 160 when he came and you can't

16

make that diagnosis on that. Then it went up to about

17

260, and as I mentioned I think in my evidence, they

18

can't make the diagnosis on that, the books and the

19

cardiologists say a baby that size to cause that

20

degree of illness usually it is in the 300 mark.

21

In any case, they treated him, and

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the interesting thing again was even with the treatment

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by the time he was transferred to Dr. Malcolmson at

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McMaster Medical Centre two and a half hours later,

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Dr. Malcolmson testified before Judge Vanek that he was just about dead when he arrived there, still just about dead when he arrived over to McMaster.

Well, as I said, my concerns - and the blood sugar was listed as plus or minus 25, and I don't exactly know what they mean, I take it they used some sort of a dipstick in the blood rather than a laboratory determination, I don't know, that gave that sort of range. Putting those things together, as I said, various things and diagnoses come to mind, but because there are paediatric medical emergencies I felt that the thing that would have to lead my list would be an adrenal problem.

Then the thing that goes onto that is the level, when things went down when he got to McMaster and then they started up again, and they were down again here, and then they were up again terminally.

As I have said repeatedly, I have tried to be fair in my report. I did not say he had transient adrenal insufficiency, I said he may well have had transient adrenal insufficiency. I said we are told about the digoxin and that must be taken into account and it might be this, that and the other thing.



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So that is where I stand. Now, if somebody has a better diagnosis than that I am prepared to debate it. Because someone has to come up with something that caused the high potassium on two occasions in Hamilton and terminal here.

Q. But the bottom line, Doctor, is that they made him better at McMaster but they couldn't make him better at The Hospital for Sick Children, even though you have given evidence that you thought he had the same thing at both places?

A. I don't think I said that. I said there was digoxin there. I don't think those are the kind of fair statements about "they made him better" one place and not the other. Let us say he seemed to improve there. Don't forget he didn't improve completely, there was another thing of a heart that slowed down too much, and Dr. Malcolmson referred the baby because of that.

Q. I am aware of that, Doctor.

A. Yes, and there the dig. levels went up to, as I recall, 1.8 at one time, and I think he wondered whether he might do this, I think Mr. Labow talked to me yesterday about the possibility of individual sensitivity. Two things. But in any case Dr. Malcolmson was then worrying about a sick sinus syndrome.



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Now, if there was the same condition operating that nearly killed him at St. Joseph's, that came in again at Sick Children's, then you know, your view is right, then he went on to die. But there was a complicating feature then of digoxin. We know that just as the potassium can put the digoxin up, the digoxin can put the potassium up, so there was an additional factor.

Q. I am aware of that. You have stated in fairness as well, Doctor, and I respect you for your complete candidness in this at page 3,453, line 2:

"So, all I am saying is he had - I don't know what he had. My bottom line again is I don't know because I can't prove it."
Is that a fair scenario?

A. I guess if I said that I still feel that way, yes.

Q. You still agree from two days ago, Doctor?

A. I can't remember things from one day to the next, Mr. Shinehoft.

Q. You also indicated, Doctor, at page 3,457, line 10:



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"I think we are still in the dark
ages of medicine. Although the thing
may not fit the textbook picture of
adrenal insufficiency we see some
that are on the fringe."

I was just curious to know what is your definition
of "textbook picture of adrenal insufficiency", and
I think you have given it with the blood gases
situation, have you not?

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A. No, I don't like those
blood gases.

Q. The potassium ---

A. Yes, I am sorry, the
electrolytes, yes.

Q. The electrolytes, I am
sorry.

A. True Addisons would be
that plus the sugar being low and whatever, but as
I said I think in there somewhere, and I did not
want to go into detail, the thing we see in children
is a completely different situation, a differential
action of the three parts of the adrenal gland but
just as desperate and just as fatal, early on.

I think what I was meaning in that
is it was more related to the enzyme things that
are going to come up, and this article that is here
in print, it is a very interesting one because the
baby was not too unlike Kevin Pacsai, as far as I
can make out, in the French here, early on, and they
got him over that episode and got him on adrenal
hormones for the salt and water containing thing I think
for only a matter of months, and that is what I cannot
read clearly. Then at 6 years of age the baby went
on and developed the full blown Addison's picture



and yet early on showed only the one set of things.

THE COMMISSIONER: This article that you were referring to, is that before us?

THE WITNESS: No, it is not, sir, because I wanted to have it translated so I have not read it myself because I am not a scholar of French. I shall pass it to you, if I may.

THE COMMISSIONER: Mr. Lamek is totally bilingual. I have been, at great expense to the taxpayer, been educated in French too. We might manage to get through it, but then we would have the advantage over everybody else.

THE WITNESS: If you could copy it in French, could I have the French one back.

MR. LAMEK: I assure you we cannot copy it in English, Doctor.

THE WITNESS: I hope not. I am just a little unclear how long they kept him on the adrenal hormones early on, and that is where I am stumbling with my French.

MR. SHINEHOFT: Q. Doctor, you have said as well, in fairness, that you have made a provisional opinion and you say that you would defer to the opinion of people like the pharmacologists before you are in a position to give a final opinion. Is



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that correct?

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A. That is in relationship to

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the digoxin and the meaning of it, yes.

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Q. And the potassium business?

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A. If it were not for the

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digoxin I would have had no concern, I would have
said this is a potassium problem. With the dig. there

8

and the interaction between dig. and potassium which

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is just I think, although Dr. Spielberg mentioned

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it to me, it surfaced, I think one of the first times,

11

from Dr. Schwartz in Cincinnati at the conference

12

which I attended with Mr. Lamek.

13

Q. So the people that you are

14

referring to are people like Dr. Kauffman who is

15

going to come and give evidence here?

16

A. Yes.

17

Q. We have the benefit, Dr.

18

Bain, of having part of Dr. Kauffman's report and

19

I would like to read to you part of it as it relates

20

to the baby Kevin Pacsai, for any comment that you may

21

have. He says at page 8 or page 312, whichever page

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you would like to pick ---

23

THE COMMISSIONER: This is not yet

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an exhibit, is it?

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MR. LAMEK: It is not an exhibit, Mr.



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Commissioner. It is again one of those documents that have been distributed to everybody.

THE COMMISSIONER: I just wondered how it got to be either 8 or 312.

MR. SHINEHOFT: Because there are two numbers.

MR. LAMEK: I think Mr. Shinehoft is referring to the page number, not the exhibit number.

MR. SHINEHOFT: There are two page numbers, Mr. Commissioner. That is my reference.

THE COMMISSIONER: I see.

MR. SHINEHOFT: Q. Dr. Kauffman in his summary and evaluation of Kevin Pacsai, in the second paragraph, states:

"The premortem serum level 5 hours prior to death is consistent with the post-mortem concentrations of approximately 25 ng/ml and the actual serum concentration at the time of death was probably somewhere between 10 and 20 ng/ml. This is consistent with a toxic dose of digoxin. The hyperkalemia observed three to four hours prior to death is also consistent



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"with digitalis toxicity. Abnormally high digoxin concentration as well as hyperkalemia could be due to renal failure. However, this is unlikely. The blood urea nitrogen was normal and although the creatinine of 1.3 ..."

A. Creatinine.

Q. Creatinine, is it 1.3

Doctor, or 13?

A. 1.3, it should be.

Q. "...1.3 was slightly elevated for an infant this age, it does not reflect renal failure of a severity to cause this degree of hyperkalemia."

Do you have any comment about ---

A. No, he is not saying anything very much different from what I have said. Let us try to back-track over what you have said he has said. He talks about the level of 10 being consistent - or it could be 10 to 20. Taking into account the 26, was it - that means he is applying a multiplier factor pretty low, somewhere around that 2 mark, and I think he will be prepared to say when he comes, I was not going to say this, but the other day when Mr. Olah asked me about the



1
2 multiplier effect and I rather quickly said that
3 I accepted mainly around the 2 mark but I thought
4 there were levels of 4 to 10 times, then he
5 challenged me on it and I could only find notes that
6 took me up to 4.

7 I have since - I went to a lecture
8 the next day with Dr. Spielberg and he used the same
9 figures, 4 to 10, and I have said you had better put
10 your money where your mouth is on that one. He said
11 that Dr. Phillips had in fact testified here with
12 pairs that he had done not so long ago, and I think
13 the highest he had was 6.8 as a multiplier effect,
14 excluding Gary Murphy where it was about 14 or 15.
15 Gary Murphy will undoubtedly come up later.

16 So all I am saying, Dr. Kauffman
17 would appear to have taken a very low multiplier
18 effect. I have taken a kind of a medium one, just
19 a shade over 2, and I do not think there is any
20 magic to that at all. So what I am saying is that
21 the 10 and the 26 probably do coincide. He is
22 saying that the 10 may have been 20.

23 Q. He has said it may be as
24 high as 20.

25 A. Sure, but that is a guess.

Q. He also says that those



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levels are consistent with digoxin toxicity?

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A. Certainly. We have said that anything over 4 and 5 usually show toxicity but on the other side of that coin I said it is not necessarily consistent with being fatal. That was the point I was trying to make.

8

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Q. But you are prepared to concede, Doctor, that this baby could well have died from digoxin intoxication?

10

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A. I think that is the decision, that is where I ended up last July, that I thought that that answer was going to have to come from the people who are or will be expert in the field.

14

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MR. SHINEHOFT: I want to thank you, Doctor, very, very much for coming and giving your evidence, and I appreciate the candor with which you have answered my questions.

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THE WITNESS: As I have said, I do not know what - my bottom line is I do not know and I think everybody is trying their best to find out answers, and I feel as strongly as everyone else that I would like to help in that regard, whatever way.

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MR. SHINEHOFT: Thank you very much, Doctor.

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THE WITNESS: Thank you.

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THE COMMISSIONER: Thank you, Mr.

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Shinehoft. Mr. Roland.

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RE-EXAMINATION BY MR. ROLAND:

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Q. A couple of questions,

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Dr. Bain, dealing first with Jordan Hines. Mr.

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Tobias took you through some parts of the Hines

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chart to indicate the presence or absence of

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notations of apnea while Jordan Hines was in the
Hospital and you have indicated that, as I recollect

11

in your evidence, that there were periods of apnea

12

and you looked at the nurses notes. One document

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you did not look at, that was not brought to your

14

attention, in Exhibit 103 was the flow sheet on page

15

81 of the exhibit and it shows on the 7th of March,

16

1981, that there was noted ---

17

A. Where is that - is there a
number on that?

18

Q. Page 81 and right at the

19

bottom of the Jordan Hines flow sheet it indicates

20

that there was a period of apnea, or a spell of

21

apnea noted by the nurse.

22

A. Yes, there seems - I don't

23

know what was below that, whether it was a number

24

or not, or seconds, or whether it is a signature,

25



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2 but mine is blanked out.

3 Q. We may have to look at the
4 original.

5 A. It doesn't matter - thank
6 you.

7 Q. I take it that is another
8 indication that you were telling us you thought you
9 had found in the chart indicating those periods of
apnea?

10 A. I don't honestly recall.
11 I take it as that but it is a year or more ago since
12 I looked at it. I guess I was saying that I would
13 not have put it down unless I thought I had found
14 it.

15 Q. Now, dealing with Kevin
16 Pacsai, I have done my calculations of the child's
17 birth weight because Mr. Shinehoft has indicated
18 that his calculations are that Kevin Pacsai gained
19 25 grams per day and we have a birth weight in the
20 chart at page 59 of the Pacsai chart of 3860 grams.

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THE COMMISSIONER: I know what is going to happen here. Children go down, babies go down in weight immediately. So, 25 grams per day could easily be true depending on what ---

MR. ROLAND: What day you're looking at?

THE COMMISSIONER: From when to when.

MR. ROLAND: Well, just to do the calculations of the average during the life of Kevin Pacsai ---

THE COMMISSIONER: I'm not a medical expert but I do remember children, I had one child that practically disappeared.

MR. ROLAND: Q. Well, let us just do the average. We don't know the birth weights day to day from this record but certainly the average indicates at page 59, as I understand it, the birth weight is 3,860 grams and at death shown at page 96 of the chart it is 4,175 grams for a net increase of 315 grams and as I read the chart Kevin Pacsai lived 25 days from the 15th of February to the 12th of March, '81 and that is an average per day of about 12.6 grams. I take it that is consistent?

A. I can't even think in grams,



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Mr. Roland.

Q. You can't, I see.

A. I have to confess. But I think my point was that one can argue things both ways and I don't know what the good Lord, you know, intended for Kevin Pacsai, whether he was going to be a big strapping person who remained in the 90 percentile.

My point was merely that he was born in the 90th percentile and if one calculates that he was supposed to stay there then there was a net loss that he slipped a channel or a couple down to the 50th. But as I say, I don't know what the good Lord had in mind. So, my feeling was that the failure to thrive situation was very definitely possible.

Q. And as I understand what you have just told us you can't, like many of us, think in grams, so, you can't tell us whether that average is consistent or not consistent.

A. Well, the real problem is, as the Commissioner said, is in that newborn period that babies lose a whole lot of weight and then once they do start to gain then what we usually find is that they - well, don't get me on this - I keep thinking an ounce a day is sort of -- how many grams in an ounce?



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Q. I have no idea.

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A. You see, those factors of when they do start and then he did have an illness where he obviously dropped back again and there are so many confounding variables in that I think. So, all I tried to do was simplify it by looking at where he was when he was born and where he was at that time percentile-wise, channel-wise.

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Q. All right. Let me just turn then to one other topic dealing with Kevin Pacsai and that is your thesis that Kevin Pacsai may have suffered from transient adrenal insufficiency. As I understand your thesis, just to summarize it, that there are at least three incidences of high potassium: one at St. Joseph's, one at McMaster and one at the Hospital for Sick Children. Your thesis of transient adrenal insufficiency explains each of those high levels of potassium. Am I correct so far?

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A. Well, yes.

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Q. It is one explanation for the high levels of potassium.

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A. Let's say adrenal insufficiency explains them.

Q. Yes, all right.

A. Okay. If he got all better we



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would have called it transient, if somebody later finds an enzyme defect that we can go back and check post mortem material we may change it to something else, that's all, yes.

Q. And you have told us that potassium is lethal at high doses and Kevin Pacsai ultimately at the time of his death or shortly before it had a very high dose of potassium.

A. High level you mean, yes.

Q. High level of potassium, I'm sorry.

A. Yes.

Q. And you then are asked about digoxin, whether digoxin could be the reason for the high level of potassium. I gather the problem you have with that explanation rather than the explanation of adrenal insufficiency is that he had high levels of potassium at St. Joseph and at McMaster when he had no digoxin.

A. Yes.

Q. And then was given digoxin at St. Joseph's and had a reading of only 1.8. So that you had a very low reading or therapeutic reading of digoxin which doesn't then explain the incidence of high potassium levels at St. Joseph's and McMaster.



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A. Well, yes, certainly if I didn't

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make that point I meant to was that there was no

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history of his having had digoxin before the high

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potassium level at St. Joseph's.

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Q. Yes. And then there is a

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reading at McMaster of 1.8 and again he has a high

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level of potassium.

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A. It starts up again, he had two

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or three low ones.

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Q. So, I take it your concern is

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that the digoxin doesn't explain in this baby those
high levels?

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A. Well, as I am saying, the things

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are there both times and I have tried to be very

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careful and very fair in saying digoxin can put

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potassium up, but likewise, potassium can put digoxin

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up. So, I am saying though that if you have had a

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couple of incidents before where it wasn't related

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then you would be going against the grain to say that

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there were three episodes all due to three different

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things. I was trying to bunch them and make a case

for one diagnosis.

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MR. ROLAND: Thank you. Those are

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all the questions I have.

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THE COMMISSIONER: Thank you,

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Mr. Roland. Mr. Lamek?

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RE-DIRECT EXAMINATION BY MR. LAMEK:

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Q. Dr. Bain, on that last point.

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A. Yes.

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Q. You say might be, I have

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forgotten the word you used, artificial or strange

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or strained to treat all three events of elevated

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potassium as being attributable to the three different
causes.

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A. Well, the thing we are always

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taught in medicine is to try to make one diagnosis.

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Q. Yes.

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A. Rather than if there are a

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bunch of symptoms to make three or four because you
would usually be wrong.

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Q. But I take it there is no

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compelling reason?

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A. None.

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Q. For ascribing the same cause

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to all three incidents of elevated potassium here.

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A. In medicine there is nothing

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that is hard and fast.

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Q. And indeed whereas you are able

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to arrive at a diagnosis of adrenal insufficiency

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with respect to the earlier episodes.

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A. Yes.

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Q. Of elevated potassium, that was in the light of other chemical findings on the electrolyte levels in serum.

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A. It was a sodium and a chloride that were low and they were a little bit more the second time and he was on an intravenous which, as I recall it, may well have tempered the picture, yes.

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Q. And he had low blood sugar the first time.

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A. He had low blood sugar the first time but that is something that, as I say, parts of the adrenal glands seem to work differentially at times.

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Q. But in the absence of comparable levels, electrolyte levels and blood sugar levels on the occasion of his death, immediately prior to his death, is there anything that even suggests that it is preferable to ascribe the same cause to the elevated potassium as you had ascribed for the earlier incident?

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A. I'm not exactly sure what you mean. As I say, I come back to the same thing that if I have a baby who has that diagnosis and the diagnosis is not made - we had a little baby once



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called Charlie E. 9, an Eskimo baby from Moosonee and they kept treating the episodes but never made a diagnosis and he came down here and the diagnosis was made in the Emergency Department but they waited for the results of the blood tests and he died of his sudden high potassium, boom. So, I don't know whether that is answering your question.

The reason for ascribing it is if you have something happen once and then a similar thing happens again then that has to be number one on your list. It is not hard and fast by any means and, as I say, I did say he may well have had, I did not say he had.

Q. I understand. I understand you seem to be preferring the same explanation for the ultimate high potassium episode as you ascribed to the original one.

A. Yes, and the more I read about it and the other things and I will be very interested to see what the clinical pharmacologists feel the contribution of the digoxin is. Dr. Phillips said to me the other day afterwards he said, you know, I am beginning to think more and more that the potassium theory is the correct one. That is an aside, he was probably humouring me.



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Q. Well, we may have to figure out which is chicken and which is egg in that one.

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A. Yes.

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Q. But is there not this difference between the two situations, Dr. Bain, that in the Hamilton episodes of elevated potassium you had certain surrounding circumstances, that is to say, depressed other electrolytes and depressed blood sugar.

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A. That is certainly true but ---

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Q. May I finish the question.

12

A. I'm sorry.

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Q. Whereas, in the Hospital for Sick Children episode of elevated potassium you did not have those depressions of electrolytes and blood sugar but you did have the presence of digoxin?

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A. But we did have slight depression and that is why I will be interested when you translate this article because he was postulating primary hypoaldosteronism, which is just a salt and water retaining one like this and I think there is a little statement in there that it says that the carbohydrate metabolism may be involved. This is one of the reasons I didn't speak to that. But nevertheless, there were other things, as I say,



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in trying to put things into one mould and I did say that perhaps the sodium and chloride were because he was getting that intravenously.

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Q. Yes.

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A. And again you will find in his article, I was very surprised in his case when they first made the diagnosis, his levels of sodium chloride weren't as low I don't think as Kevin's.

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Q. But certainly by the time we are looking at the Sick Children's Hospital episode of elevated potassium we have a new player in the game and that is a known elevated digoxin level?

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A. Correct, you're absolutely right. Well, did the potassium put it up, it was there but we will say it was there.

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Q. Who knows how it got there but it is there, is it not?

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A. Correct.

Q. All right. And as you say as to which is the chicken and which is the egg we may have to ask the pharmacologists and hope that they have the answer.

A. I don't think they will, but maybe.

Q. However they identify the parent



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and however they identify the child.

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A. Yes.

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Q. That is a player in the game
that was not present in the Hamilton situation.

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A. Absolutely.

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Q. All right. And it may be I
take it that the elevated potassiums on the two
occasions are attributable to different causes.

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A. That's always possible, yes.

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Q. Now, can we go back to something
that Mr. Strathy raised with you in the course of his
cross-examination? This, Mr. Commissioner, is found
in Volume 61 at pages 3602 to 3. Mr. Strathy was
asking you about the 14 children whom you had placed
into your Group 1B, about whom questions had been
raised either by the chart or perhaps in some occasions
by yourself?

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A. Yes.

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Q. And it is clear from your
report and from your evidence that with respect to
11 of those 14 children you had been able to satisfy
yourself that the question could be satisfactorily
resolved and these children could in effect be
treated as Group 1A children?

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A. I believe that is so.

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Q. But there were three about whom some possible question remained with respect to drug involvement?

A. Yes.

Q. They were Velasquez, Gosselin and McKeil?

A. Yes.

Q. And Mr. Strathy suggested to you at page 3602 that each of those children was in any event at serious risk of dying exactly when he did. Do you remember him putting that to you?

A. He probably did. There are so much there. If you tell me he did I believe you.

THE COMMISSIONER: Oh, yes, that is at page 3603.

MR. LAMEK: Yes, 3603.

THE COMMISSIONER: But that is almost a direct quote from Dr. Bain's report?

MR. LAMEK: Yes. The question was:

"Q. So, it is your opinion on all three of those..."

That is Velasquez, McKeil and whoever the third one was.

THE COMMISSIONER: Gosselin.

MR. LAMEK: Gosselin.



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"...that whatever was ultimately responsible for their deaths they were at a serious risk of dying exactly when they did."

And you gave a rather long answer, Doctor.

A. Yes, I think I would have because I would have a little trouble with Velasquez I think myself.

Q. I would have hoped so and indeed that is what I wanted to clarify.

A. Yes. Yes, because I don't think, you know, he was postoperative and he was doing well and, you know, the very fact that I attributed it to something else.

Q. Yes.

A. And I have forgotten where he was put in the risk classification by the others, I don't think he was in a 4D or anything by the others. No, I would certainly agree with you on that.

Q. Indeed, so far as Velasquez was concerned it is fair to say is it not that he was not expected to die at that time?

A. That's right. That's right, yes.



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Q. People were looking forward to sending him back to the Islands?

A. That's right, yes.

Q. In good shape?

A. No, I felt this was because of the note I read you from the resident the other day that there seemed to be a cause and effect there.

Q. Certainly. Now, while we are referring to Velasquez, Dr. Bain, Dr. Rowe has said, and this evidence, Mr. Commissioner, is found back in Volume 11, page 1935 to 1936. Dr. Rowe has said that although he subscribes to the idiosyncratic reaction to Narcan theory of the cause of this child's death, he has said that nonetheless his death and the manner of his dying was consistent with digoxin intoxication and that digoxin toxicity may be as plausible an explanation of the death as the idiosyncratic drug reaction.

I ask you, Dr. Bain, do you see anything in this chart that suggests that the death of Velasquez may not be consistent with digoxin intoxication? Would you like to look at the chart?

A. No, I don't think so because, you know, I have agonized over that point and I must say early on in some of the sessions I sat in on I



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3 wasn't happy with that sort of line of thought because
4 I think one day the Commissioner said something along
5 the line, well, if it were a motor vehicle accident
6 you would see some evidence of it and, therefore,
7 it would be consistent with - well, I would put forward
8 that you could have a motor vehicle accident and have
9 the baby shaken and a subdural hemorrhage and those
10 things where you wouldn't think of it at all.

11 Now, what I am saying is that unless
12 there is something to make me think of digoxin, you
13 know, and there was nothing in the history, there
14 was nothing, and I must say, as I say, I had the
15 benefit of the trial transcripts from the other and
16 there was nothing from Mr. Cimbura or anything about
17 any dig. levels.

18 I assume that since the baby had had
19 a post mortem examination that specimens were
20 available to Mr. Cimbura and that he had either done
21 them and not reported them or whatever, I don't know
22 that, but the baby did have a post mortem and we do
23 keep tissues.
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So I assumed that there was nothing in dig., and you know, if you are asking me the question about; is it compatible with extra strength Tylenol, I have to say, you know, the same sorts of things, and I don't like saying that unless there is something that says it and that is the reason.

Q. My question in fact, Doctor, is rather directed to the other point; because as I understood Dr. Rowe all he seemed to be saying was that, sure, the fact that this child died suddenly, unexpectedly in the way that he did is consistent with digoxin intoxication. My question to you though is different. That is to say, do you see anything in the chart which suggests to you that this death was not attributable to digoxin intoxication?

A. Well I saw what I thought was the fact that here is a patient who has pain, who is given codeine, who gets drowsy, and who is given naloxone, who improves.

Q. Yes.

A. So if his demise, or impending demise were due to digoxin, why would it improve with naloxone? And so, and the second dose of naloxone within a minute he is dead. So that,



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2 you know, I could not put those - I could not state -
3 unless there is something that those clinical
4 pharmacologists have that naloxone does something
5 to dig. and I have not seen anything like that in
6 the literature.

7 Q. If I understand you
8 correctly, Dr. Bain, you are suggesting that the
9 response to the first dose of naloxone ---

10 A. Yes.

11 Q. ... is in your view perhaps
12 inconsistent with the child at that stage suffering
13 from digoxon intoxication?

14 A. I say it is inconsistent
15 with him suffering from anything other than an
16 opiate, or whatever reaction, for which naloxone is
17 the antidote.

18 Q. And we come next to a number
19 of questions that were put to you in the context of
20 discussions about Baby Justin Cook. Miss Symes asked
21 you if the baby having had a blue spell at about
22 6:00 p.m. on the evening of March 21st, if another
23 blue spell at 3:45 a.m. on March 22nd was not
24 unexpected, and your answer was - and that is found,
25 Mr. Commissioner, at Volume 61, page 3663.

A. I hope I said yes that it
was expected; or yes that it was not unexpected.



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Q. The question begins at

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line 6:

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"Q. Given the problems that had occurred, that is the blue spells on admission, and the blue spell that occurred at 1800 hours, is it fair to say Dr. Bain that another blue spell was not unexpected?"

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And your answer was:

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"A. Oh, insofar as blue spells in tetralogy there is no predicting when they are coming. Certain things will precipitate them but they may come on their own and you can't predict, so, yes."

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A. Yes.

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Q. And then you say "No, not

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at all unexpected".

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A. Correct.

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Q. I don't necessarily

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challenge that concept, Dr. Bain, believe me, but

21

I do want to clarify: Justin Cook so far as I understand it was not a tetralogy case, was he?

22

A. No, I agree with that,

23

but he had the same out-flow sort of problems that

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does give you blue spells apparently.

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Q. As I say I am not challenging you, I wanted to clarify it.

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A. No. I think that is a point well worth clarifying, because it brought up the point earlier on, he should not have got dig. Well, maybe in retrospect it wouldn't have been contra indicated, I am not sure of that, although he did have some out-flow problems. I have a little trouble with indications and contra indications.

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Q. Well certainly with respect to that, as I recall it the evidence has been here, of Dr. Freedom, that after having performed the catheterization it was his opinion that digoxin was contra indicated?

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A. You see I didn't hear that.

Q. In any event the fact the child didn't in a strict sense have tetralogy of Fallot here doesn't affect your view that having had one or two prior blue spells another was perfectly in the cards?

A. Yes.

Q. Now, with respect to the second blue spell in the early hours of March 22nd, Dr. Bain, you told Miss Symes, and this, Mr.



1
2 Commissioner is found at pages 3664-5 that in light
3 of the earlier good response to Inderal on the
4 occasion of the 6 o'clock in the evening spell you
5 were surprised that Inderal didn't again help the
6 child.

7 A. If I said that it is pretty
8 close to what I meant, yes. I think aside from
9 individual variations in response I think every one
10 would have thought he would have responded, yes.

11 Q. If it worked once the
12 likelihood was that it would work again?

13 A. Yes, the likelihood, 99
14 per cent on that sort of because there is patient
15 variability.

16 Q. It is plain that the Inderal
17 and the 3:45 episode did not?

18 A. Did not.

19 Q. And Miss Symes therefore
20 asked you: If the medication administered at 3:45 a.m.
21 were not Inderal but was in fact digoxin, whether
22 that would explain the absence of a response of
23 the kind expected from Inderal; and you very
24 properly said you are not going to get an Inderal
25 response if you are not giving Inderal.

A. Yes.



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Q. And I have to ask you this, therefore, Doctor. If a large dose of digoxin, perhaps one or more adult vials had been administered to Justin Cook prior to 3:45 a.m., are you able to tell me whether that could, or would, interfere with or impair the effectiveness of the Inderal that was given at 3:45?

A. I am sorry, I can't, I have just never thought of that before and I can't answer that.

Q. You can't tell me therefore whether if Justin Cook was already suffering from the effects of digoxin toxicity at 3:45 a.m. that would explain the lack of response?

A. Certainly, you know many - I am just trying to think of circumstances. I know in the old days we certainly probably had - before we found out that kids shouldn't have dig. we had them on it at times, and when Inderal did come in it worked in the face of that but I don't know what it would do in the face of a massive dose.

Q. On that same topic, Dr. Bain, Mr. Strathy asked you about the possibility of confusion of vials of medication.

A. Yes.



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Q. And your answer if I may say so was a prudent one; this is found at page 3631, Mr. Commissioner. Mr. Strathy put to you certain evidence that had been given by Dr. Spielberg, and then at page 3631 you said:

"Let me ask you first, do you agree that vials of digoxin resemble vials of many different emergency medicines?" And you as I say prudently said:

"I cannot answer that. I would suspect so because there are a limited number of vials. I think what has to be done, if it has not been done by the Commission, perhaps far be it for me to suggest, but to get a bunch of vials and look at them. I plan to do that myself; I have not done so." I wonder if you have had a chance?

A. I still have not had a chance.

Q. Let me help you with a couple of them, Dr. Bain.

A. Yes.

Q. We keep these things very secure as I understand it.



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A. They showed me some the other day and I have forgotten which they were already.

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Q. We have a variety of things here and I have to give an oath every time I handle them that I will put them safely back.

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THE COMMISSIONER: Put them back I trust in exactly the same manner.

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MR. LAMEK: Yes you may count on it, Mr. Commissioner.

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THE COMMISSIONER: Which exhibits do you have there?

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MR. LAMEK: Now, that Mr. Elliott will have to tell me.

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Q. Exhibit 222 is one.

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A. 225 is on this one.

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Q. I am sorry, 224, 225, and then the others are vials of the adult and paediatric preparations of digoxin.

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THE COMMISSIONER: They are 225, 224 and 131.

Q. We have got first of all, Dr. Bain, and I am sure you recognize the ---

A. I don't recognize any of them, Mr. Lamek.



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Q. Let me hold them up in front of you then. I am showing you first the adult preparation of parenteral digoxin I think is on there.

A. I am a menace trying to read these things.

THE COMMISSIONER: Is that Exhibit 131?

MR. LAMEK: That I believe to be 131, yes.

THE COMMISSIONER: Yes.

Q. And then the paediatric preparation for parenteral. We have in Exhibit 224 a number of different medications, atropine also in a clear vial and presumably therefore capable of being mistaken at a glance for the other clear vials.

A. Those, as I say with the red/green colour blind person.

Q. Yes. Adrenaline similarly in a clear small vial?

A. Yes.

Q. I don't know whether I am permitted to take these out, but I am going to do it anyway, there have to be some perks attached to my office.

A. To the job, yes.



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Q. I am showing to you now a vial of Inderal, Dr. Bain.

A. Yes.

Q. And I am putting it beside the two digoxin preparations. I ask you first, can you tell me what you considered to be the likelihood of confusing those two vials?

A. Well I guess if one knew what they were in, that would be fine, I suppose if ---

MR. ROLAND: Mr. Commissioner, in fairness I stood up and objected to this very question when Miss McIntyre asked it. I said we can all look at them and decide ourselves. If my friend wants to take a poll of everybody in the Hospital, or out of the Hospital and decide to ask, would you confuse this, would you confuse that, it is interesting, but I think it doesn't help us much.

What I think helps us in the issue of error is what the literature tells us about confusion about like vials, and unlike vials and so on, because studies have been done. But the impressions of one or other of us doesn't seem to advance the exercise very much at all. I object to that question with respect when it was asked by Miss McIntyre and you agreed with me. Now Mr. Lamek



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2 is coming back and doing the same thing. I mean, it
3 is an interesting exercise but I don't think it helps
4 you.

5 THE COMMISSIONER: Do you not think
6 perhaps Dr. Bain would be a little better qualified
7 than most of us?

8 MR. ROLAND: Well I am not sure of
9 that, he may or may not. As I understand it Dr. Bain
10 is not giving medications, that is not part of his
11 at least recent medical experience.

12 THE COMMISSIONER: He has been around
13 hospitals.

14 MR. ROLAND: Yes.

15 THE COMMISSIONER: He has been around
16 hospitals quite a few years and we haven't, and that
17 is why I thought he might be asked, it wasn't my
18 idea.

19 MR. ROLAND: It is not the confusion ---

20 THE COMMISSIONER: Mr. Lamek is doing
21 this on his own.

22 MR. ROLAND: If the issue is would
23 Dr. Bain confuse them or not, or would a person like
24 Dr. Bain in his position confuse them, that is a
25 useful question. I don't think that is what the
issue is in terms of confusion. It is not from an



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eminently qualified doctor like Dr. Bain but from
nurses.

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THE COMMISSIONER: I agree with you.
Nurses might be even better.

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MR. ROLAND: Well it is nurses or
treating physicians, residents and so on who are
actually administering it.

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THE COMMISSIONER: There is a good
deal of merit in what you say, but I am going to
allow the question anyway because Dr. Bain has been
around hospitals and he might be able to help us.
I am not being offensive, Dr. Bain but I won't
necessarily pay any attention to what you say if
I find the two vials are readily distinguishable
and you say they are exactly alike, and I don't
think so. Mind you I think your eyes are a little
better than mine at this moment but I can't be
sure.

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THE WITNESS: Do you want to bet on
that, sir?

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THE COMMISSIONER: All right.

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THE WITNESS: You will lose.
Q. It was after all, Dr. Bain,
you who said you really have to look at them to
decide whether they could be ---



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A. I think my point before is I have gone through the business of colour coding and all of those things, and I have said one must read what is on it because all the rest goes out. If you ask me does the brown look different from a clear one, my answer is, yes.

THE COMMISSIONER: I am sorry, your answer was what?

THE WITNESS: Does brown look different from clear to my eyes and the answer is yes, but one must read the writing.

Q. And similarly, Dr. Bain, I am showing to you a vial of what is described by its label as Furosemide or lasix?

A. Yes. It looks not unlike - I suppose one might pick up those two, even though they are different sizes they are both brown.

Q. When you say those two you are referring to the lasix and the Inderal?

A. Yes. Then I guess what one has to know, and maybe this is why I said we need to get everything done. Different companies make different things and I don't know whether this represents the full spectrum of the vials that are in the Hospital for Sick Children or on the wards.



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2 Perhaps it is so, but if not that is why I felt that
3 one should in fact look at them. But I will come
4 back many times, because as I have said I have sat
5 on committee, after committee, after committee when there
6 have been problems of trying to figure ways, and the
7 pharmaceutical companies have done the same, somebody
8 gets in a big kick about colour coding, and then two
9 companies colour them the same way and they are
10 different drugs, and like the Vitamin E epinephrine
11 thing that you are in difficulties.

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So I think everybody keeps coming back, that one must pick it up and read it.

Q Doctor, I have no doubt that is right and I recognize of course that anything can happen and the craziest mistakes occur.

A. Yes.

Q I guess all I am asking you is in light of what you said, you would have to look at them, whether you can give me your view as to whether it is likely that those would become confused?

A. Well, a brown and a white, I would have some difficulties. My problem on that one, Mr. Lamek, I am not trying to hedge, I am not clear in my own mind how that Inderal that was taped to the bedside, I believe they had to go and borrow it somewhere, and whether they drew it up on the other ward and then brought back a clear syringe with something in it and taped it, this is what I don't know.

Q They may have, Dr. Bain, but is it not fair to say that however and wherever that was drawn up, it was drawn up at some point from a vial?

A. That is absolutely true, but if somebody who drew it up and then in a clear syringe,



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and I take it that fluid itself is clear inside, is it, rather than brown, and then came back and put a couple down on a thing and then picked up the wrong syringe, you know, I am not trying - I am just saying that crazy things happen.

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Q. That is possible. We don't know whether that happened?

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A. Yes.

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Q. Mr. Strathy also asked you about the possibility of error in what he called a highly stressful situation, referring, as I understood him, to resuscitation efforts. You said it was certainly possible that a drug error could be made in those circumstances. Do you recall, that is at page 3633?

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A. Yes, I am sure I said that.

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Q. So far as the obtaining of the Inderal from another ward was concerned, I have no information or evidence to suggest that that occurred at a time of particular stress or excitement or panic, have you?

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A. No, I do not.

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Q. Therefore whatever may occur in the frenzy of resuscitation effort there is nothing to suggest that that was the atmosphere in which the



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Inderal was obtained from another source?

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A. No, I believe it was taped to the bed so it must have been there beforehand.

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Q. With respect to what may or may not have occurred during the resuscitation effort on Justin Cook, will you agree with me that in order for a drug error to have occurred during that resuscitation effort, we are not talking simply about a drug error, selection of one drug for another by mistake. We are talking, are we not, Dr. Bain, about a whole string of errors and anomalies that would have had to occur?

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A. I am not certain of what you are saying, so go on.

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Q. You know, sir, do you not, that Drs. Costigan and Mounstephen in the late evening of March 21st --

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A. Went around, yes.

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Q. Went around, and indeed reported that there was no digoxin on the crash carts in 4A/B.

A. Yes.

Q. In order for there to have been a drug error involving digoxin on that crash cart during resuscitation, they would have had to make a mistake in the first place?



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A. Correct.

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Q. Second, it has been our understanding, and I think Dr. Rowe gave this evidence, that digoxin is not something that is normally found on a crash cart, certainly on the cardiology wards. Is that your understanding?

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A. That - but as I say at that time I guess it was found on crash carts in various parts of the Hospital.

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Q. Not on the cardiology wards?

A. I don't think they found any in Cardiology, in my recollection, yes.

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Q. Indeed Dr. Rowe's evidence as I recall it was that he would not expect to find any.

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A. Yes.

Q. And therefore if there was digoxin on the crash carts on that ward on the night of March 21 to 22 it probably should not have been there in the first place. Is that fair?

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A. I would certainly have to look at the list of what they are supposed to have on those crash carts, I think Dr. Rowe was to bring that down to you one day and I don't know whether it ever got here or not. So I don't know that.

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Q. Yes, I think we did get it. It



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is not included.

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A. If it is not included in the list then one would have to say that it was not considered in the group at the time.

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Q. Third, if I understand Dr. Spielberg's evidence correctly, what was on the crash cart and missed by Mounstephen was not merely digoxin but it would probably have had to have been an adult vial of digoxin?

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A. If he said that, I think - I am not entirely sure why he would say that because I think I did mention, I don't know whether it was to you previously or somewhere I did ask, some months ago, I asked Dr. Spielberg's helper, Dr. Rajchgot, whose name I can't spell, Percy Rajchgot, what sort of dose of digoxin would one have to give to a baby of the weight of these babies - Cook - Kevin?

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Q. Justin.

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A. Justin, I am sorry, I knew I was blocking somewhere, Justin Cook's weight, what dose would have to be given by push to give you a level of 70 was my specific question, and his specific answer was that the loading dose for his age could he thought do it, which would be the paediatric vial, and the loading dose is usually half.



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So that is all, so I am a little surprised at that
and that is something for the clinical pharmacologists,
I think.

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Q Let me be plain so that you
understand where I am coming from on this, Dr. Bain.
Dr. Spielberg in his evidence said that something
less than a paediatric ampule could produce that level
if it were administered almost at the instant that
circulation ceased. In light of the concentrations
of digoxin in the fresh heart tissue of this child
he did not conceive of that as a viable proposition.

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A Again, then, I won't bow to
that because I think again that comes into the fact
that must be debated because, again, the fresh tissues
that they did for some reason were just RIA, they
did not use HLPC; whereas on their fixed tissues they
did use HLPC.

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Q I won't argue that one with you,
Doctor. All I can is the only clinical pharmacologist
from whom we have yet heard, and I understood you
were bowing to their opinions on these things --

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A Some things. As I told you, I
have some stupid questions to ask from them.

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Q -- has told us that in his view
what can best be reconciled with the tissue



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concentrations and blood levels is administration
at a point sufficiently distant from death to be
something less than a single adult vial?

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A. I would certainly bow to that
on the point and I am sure what Dr. Spielberg says,
accepting the numbers, that is the 1177 in the
tissue and the 72 in the heart, that would be his
conclusion.

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Q. On a minor matter of correction,
Dr. Bain, the measurements in the fresh tissue were
HPLC and RIA?

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A. That other thing I have from
the --

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Q. That was Mr. Cimbura's evidence
here a couple of weeks ago.

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A. I am sorry, the CDC I think says
otherwise. I guess something is wrong.

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Q. So we would have had to have
had digoxin on the cart et al. It would have had to
have been, in Dr. Spielberg's scenario, an adult vial
of digoxin and would have had to be missed by Mounstephen
and Costigan in their search.

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Fourth, obviously someone would have
had to pick it up by mistake for some other drug. Do
you agree with that?



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A. Yes.

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Q. And fifth, as we understood

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Dr. Costigan's evidence about the procedures to be

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followed in administering drugs on resuscitation, the

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physician who administered that drug would have had

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to err in departing from procedure either in not

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asking that the vial be produced to him along with

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the syringe or not reading the vial if it were

produced to him?

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A. Correct.

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Q. In other words, Doctor, we are

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not talking about a medication error, I am suggesting

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to you, we are talking about the coming together of

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five very different things, are we not?

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A. Yes, that is true.

16

Q. Do you have a view on the

likelihood of those five coming together?

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A. All I can say to that, and I

18

guess the thing that jumps into my mind since I am in

19

the chair here and under oath, I think I remember

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fairly vividly Mr. Cooper making the same argument

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in front of Judge Vanek on the basis of the Vitamin E/

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epinephrine mixup at Sick Children's because there

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were two or three different nurses and each supposed

to check it twice and have somebody else check it.

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I think the number he arrived at was 6. Yet it did happen. So if you are asking me the likelihood, I would hope it would never happen, Mr. Lamek. I am saying on the basis of things that do happen --

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Q. Doctor, I say to you again, I acknowledge the possibility that anything can happen, no matter how outlandish it may seem.

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A. Yes.

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Q. In terms of likelihood?

A. The likelihood goes down with

every --

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Q. Every layer that you add on?

A. Every check that is done, yes.

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Q. There was another area with respect to medication errors, Dr. Bain. Miss Symes asked you about Exhibit 248 which you remember was the paper in which people had demonstrated their rather remarkable inability to calculate proper doses?

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A. Correct.

Q. Reviewing the charts of all these children, Dr. Bain, did you check whether the doses of digoxin prescribed were appropriate and properly calculated?

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A. No, I did not.

Q. Did you make any inquiry about it?



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A. No, I did not.

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Q. I tell you, Dr. Bain, that we

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have heard no suggestion in the evidence here from

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anybody that any order for digoxin in the charts

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was excessive or in any way improperly calculated.

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That is not to exclude the possibility of mis-

8

administration or mispreparation?

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A. Or if somebody made the mistake

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they may not have known it. Unless it was a lethal

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Q. I tell you frequently in

12

referring to the orders for digoxin the cardiologists

13

said perfectly proper dose, perfectly proper dose.

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A. Yes.

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Q. So there is nothing that you

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have in mind or nothing that you are aware of to

17

suggest that errors of the kind referred to in

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Exhibit 248 may have occurred with respect to any of
these children?

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A. I hate to confess this under

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oath but I would suggest on that paper - I had not

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read it as you recall when I entered it the other day

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and I took the opportunity of reading it on the

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weekend, and they are all simple arithmetic questions,

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nothing to do with medicine. I would like the

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Commissioner, perhaps, or you, Mr. Lamek, to ask for volunteers in the same way here to work those out. The one thing it did not say was the time allotted and I decided I would do it on the weekend under a very stressful - my grandson was there and just when I came to Question 3 the phone rang and my wife handed me this two month old baby who was screaming, and I made a mistake and it was a lethal mistake.

Q. In the calculation.

A. I put the decimal point - it should have been point-33 and I put it at 3-point-3. Normally I go back and check things a hundred times. I said, you know, that is pretty close to the situation that would have happened with a nurse. The babies are screaming and the phone rings.

So I would challenge everybody in this court sitting here today to do that test and be honest with yourself or perhaps if the Commissioner thinks they could do it anonymously before we adjourn today, I think you would find quite a few errors.

Q. Doctor, if I were to try that, I would fail miserably.

My question to you however was a rather different one and that is, is there any information that is available to you to suggest that



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any of the doses as ordered were miscalculated?

A. To the best of my knowledge there were no incident sheets made out and there should have been if that happened.

Q. Finally, with respect to medication errors, I am interested in the answer that you gave Mr. Olah and this is found at page 3697, Mr. Commissioner.

Mr. Olah was putting to you certain passages from Exhibit 248 and asking for your comments. He referred at the beginning of line 7 or 8, page 3697, to the following paragraph in that article, and he read it: "Almost half of the errors were major and, in 8 cases, they would likely have been lethal. The proportion of nurses who made errors increased with the length of their professional experience." He asked; "Does that result surprise you or does it coincide with the experience generally you find in major hospitals?" I suspect he was addressing himself to the apparently higher propensity of experienced nurses who make mistakes. Your answer was:

"It would surprise me because all I can base these things on is my own experience through the years, and thinking of -- they say those things



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"could have been fatal, I have to struggle to think of things back over my forty years of where, in fact, a medication error did result in death."

I take it, Doctor, that that is great good fortune, but I do take it from that that fatal medication errors in your experience at least, and it is a long one, are very unusual?

A. I was trying to think of names and things where it had happened because those things always trigger a call to the coroner and a coroner's inquest. So over 40 years and 200,000 patient days, it adds up, 25,000 admissions a year, and I would at least have heard of them up until the time I quit as chairman, which was in 1976.

I cannot think of them so maybe my memory is failing.



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Q. I would think it is the kind of thing that sticks in your memory if it happens?

A. It certainly does.

Q. Because it is unusual.

A. It is unusual. I think it is probably off the subject a little bit but I would like to say about that study down there, over there in Israel that, and they pointed out as they went along, was that the thing that was necessary was that everything had to be double checked and then constant refresher courses and I think that is the secret, that is something that we do and that is something that I do. I am the worse worry wart when it comes. When I used to be in practice in Sudbury and I had to give a medication in the home or anything like that and figuring it out, even penicillin and things I would probably do the mathematics about 10 times. I think that is the safety thing.

So, I suppose experience to people, you might get to thinking, you know, the answers and take shortcuts, I don't know, but still hopefully the check system would catch it.

Q. The basis of your long experience in a major hospital over, as you have said, hundreds



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of thousands of patients and there were presumably millions of drug administrations.

A. Yes.

Q. Is that fatal results from drug error are more mercifully extremely rare?

A. Yes.

Q. Now, almost the last topic, Doctor, and perhaps we can go on so that we can release you when we break rather than bring you back.

A. I would be your eternal friend.

Q. The puzzling question of the incidents of convulsions or seizure-like activity of one kind or another in these patients.

A. Yes.

Q. Doctor, does seizure-like activity indicate some disturbance of the central nervous system?

A. Yes, certainly. Nervous system, I suppose central when you get into things like tetany from a low blood calcium and things then you get down to peripheral errors and things. So, let's say nervous system, yes. Now, mind you, I mean, you get me thinking, I have to hedge here a little bit. There are certain things that can be



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mimicked by seizures of stimulation of the muscular system per se without the nervous system. That is a direct effect on muscle or some rare diseases that do that, but, you know, let's not get into that. Generally speaking it reflects a nervous system.

Q. And is it your understanding, Dr. Bain, that quite apart from or in addition to any effect that digoxin may assert at receptor sites in muscle tissue, it also has an effect on the central nervous system operating through the mediation of the vagal nerve.

A. Well, I understand that, but you see, the vagal wouldn't be doing that because you are getting into peripheral motor nerves if you are going to have a convulsion.

My understanding from Dr. Fowler's article and from anything I heard the other day is that there is quite a lag before that happens and in Dr. Fowler's case it was 36 or 26 hours.

Q. Yes, I understand.

A. So, that was of concern.

Q. Well, Doctor, is there anything that you are aware of in the medical literature or elsewhere indicating what one might expect by way of nervous system effects of (a) very large doses of



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digoxin and (b), and this may be the difference of the Fowler paper, very large doses of digoxin administered to children with serious cardiac problems or impaired general health status?

A. No. I hope our library has done a MEDLARS search because when I found this out I have asked them and I keep prodding them and they have not yet come up with anything like that. I will keep looking.

Q. And notwithstanding (a) the low incidents of seizure-like activity in the Fowler study and the interval between ingestion and seizure activity, is it possible that given the circumstances of which we may be dealing here, seriously ill children and very large doses of digoxin, you might expect to find some nervous system disruption?

A. Well, this is where I have trouble because, again, Nelsons textbook which I showed you that day didn't mention that and, you know, they usually throw those things in. So, without my finding something on it, you know, again, we are at that whole thing, is it possible and, yes, it is possible but I would hate to stop doing anything that would stop thinking because I think this may be an important point.



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Q. Yes, I understand. I guess my only point is that we may be dealing with a situation here that you don't expect to find written up in the textbooks or even in the literature with any frequency at any rate.

A. As a matter of fact I did something else, I went to Dr. Swyer who is Head of our Newborn Service and I asked him in babies in this age group, they don't usually have them, they usually get home about a month, so, they are a little bit younger, I said what is their mode of dying when they don't have a brain hemorrhage or anything to suggest brain hemorrhage, brain injury when most of their problems are pulmonary ones and all and I said, you know, do they convulse and, so, he has asked most of his staff and he got back to me when I was coming down here on Tuesday I guess - yesterday, or maybe it was last Thursday and he said, no, it isn't, but I am going to - it isn't a common thing.

Q. Yes.

A. So, it is something that is bugging me there and I will keep pushing. I did have another concern and I must confess I'm working on it is that if zapping, as we refer to the term, zapping the heart causes dig. to go up what about a generalized



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febrile convulsion because we know that much of the digoxin is stored in muscles throughout the body as we heard the other day and there is a general convulsion which makes all of those muscles contract. If anybody has ever seen a convulsion then they will know how terrifying it is, does that squeeze dig. out and put them up.

So, I have hopefully got them working on that.

Q. One very last matter, Dr. Bain, if I may. Mr. Labow asked you about Paul Murphy.

A. Yes.

Q. Is it your recollection, Doctor, as I tell you it is mine, that Paul Murphy --

A. He was the older child, the older boy?

Q. Yes. And you will recall that with respect to that child there had been a decision made, an order written that he should not be resuscitated.

A. I believe that is correct.

Q. Can you tell me please the significance of that order? What does that tell me about the clinical condition of the child?

A. You are opening a terrible



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can of worms, Mr. Lamek, because the whole issue of do not resuscitate is one that I studiously avoid. I always say this is something between me and my keeper and the parents and no one besides that is going to know.

Q. I don't want to make things difficult for you, Doctor. Perhaps I can put this to you and maybe we can shorten it but by all means feel free to say whatever you think needs to be said.

A. Yes.

Q. Do I understand that if I see a do not resuscitate order on a chart it means that in consultation between physician and parents, in the case of a pediatric hospital, it has been decided that the death of that child in the short term is inevitable and that no intervention is going to make any difference?

A. And may make things worse.

Q. And may make things worse.

A. That would be the way I would handle it, yes.

Q. All right. I take it that we can't infer from the absence of such an order in the chart that the child is not terminally and irreversibly sick?



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A. No.

Q. It may only mean that the
parents have said do whatever you can for him.

A. They can't bring themselves --
yes. Well, we don't usually ask the question, or I
don't usually ask the question. In fact I usually
give all the other side of it to them. If they are
adamant - I'm not telling you what I do but I may or
may not...

Q. Yes, all right. But at least
we have heard here, and I take it it would be your
experience too that a do not resuscitate order is
certainly not written without consultation to the
parents?

A. Oh, correct.

Q. Yes. And we can at least
infer from the presence of such an order something
about the terribly, terribly serious and terminal
condition of the patient?

A. Yes.

Q. Dr. Bain, I am sorry to end
on such a somber note but those are all my questions,
thank you very much indeed.

A. Thank you, Mr. Lamek.

MR. LAMEK: Oh, yes, we should



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make the article, we have had it copied.

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THE WITNESS: Thank you. Oh, could I have a translated copy, would that be possible.

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MR. LAMEK: Our Xerox machine doesn't translate copies.

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THE WITNESS: I know, but you said you were going to.

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MR. LAMEK: I didn't say I was, the Commissioner said I was.

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THE COMMISSIONER: Well, we will see what we can do about that.

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THE WITNESS: Thank you very much, Mr. Commissioner.

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THE COMMISSIONER: The difficulty in translating though always are the technical terms but we will do what we can. Certainly we will make use of it. What number was it?

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THE REGISTRAR: 252.

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---EXHIBIT NO. 252: Document entitled: Evolution Lointaine D'Une Insuffisance Surrenale, Dite Regressive, Du Nouveau-Ne.

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MR. LAMEK: Mr. Commissioner, we started 15 minutes after the normal time, shall we



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2 take a break 15 minutes after the normal time?

3 THE COMMISSIONER: Yes, for 20
4 minutes. Thank you again.

5 THE WITNESS: I'm finished?

6 MR. LAMEK: You are, thank you.

7 THE WITNESS: Nice feeling.

8 MR. SHINEHOFT: Well, Mr. Commissioner,
9 if I could just interject for one second and perhaps
10 I might speak to Dr. Bain at the break. There was
11 a reference made to some other material yesterday and
12 I would like a copy of that.

13 THE COMMISSIONER: Which other
14 material is that?

15 MR. SHINEHOFT: It is Colonel...

16 THE WITNESS: Geppert.

17 MR. SHINEHOFT: Geppert.

18 THE WITNESS: I could give you the
19 reference if you wish and maybe then get it from the
20 library. It is the Journal of Pediatrics and it will
21 be in the library out there and I would be glad to at
22 the break.

23 THE WITNESS: Thank you, Dr. Bain.
24 I could probably speak to him at the break and get
25 that information.

THE COMMISSIONER: Yes. Subject to



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that, the quicker you retreat the happier we will be.

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THE WITNESS: Thank you, sir.

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THE COMMISSIONER: Yes, all right.

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THE WITNESS: I'm gone.

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---Witness withdraws.

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---Short recess.

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--- On resuming:

MR. TOBIAS: I was just discussing the fact that Dr. Bain had to come back today cannot be blamed on me since I was not here yesterday afternoon.

THE COMMISSIONER: No, no. Well, I think you probably still have a spot of credit left anyway. No, I think the fact that he had to come back can be blamed on me for misconduct over the weekend that resulted in -- but I must say I was led to believe by Mr. Lamek that we had only the best part of a day to go, that he obviously had not verified his sources.

Yes, Mr. Lamek?

MR. LAMEK: May I call, Mr. Commissioner, Dr. Stuart MacLeod.

DR. STUART MAXWELL MacLEOD, Sworn

MR. LAMEK: Make yourself as comfortable as possible there, Doctor.

THE COMMISSIONER: And Stuart is spelled how?

THE WITNESS: S-t-u-a-r-t.

MR. LAMEK: And MacLeod is M-a-c --

THE WITNESS: M-a-c L-e-o-d.

DIRECT EXAMINATION BY MR. LAMEK:

Q. Dr. MacLeod, you are the Head



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of the Division of Clinical Pharmacology at The
Hospital for Sick Children?

A. That is correct.

Q. Briefly, by way of educational
and professional background; you graduated from the
University of Toronto with a degree of Bachelor of
Science in 1967?

A. That is correct.

Q. And subsequently with the degree
of Doctor of Medicine in 1967?

A. Yes.

Q. And subsequently from McGill
University with a Doctorate in Pharmacology, a Doctor
of Philosophy in Pharmacology?

A. That is correct.

Q. You subsequently did an Intern-
ship at the Montreal General Hospital, and then became
a Junior Assistant Resident in Internal Medicine at
the Montreal General?

A. I actually did that before my
Ph.D.; but my medical training bracketed my post-
Doctoral training in Pharmacology.

Q. I am sorry, you are absolutely
right of course. From 1969 to 1972, that is following
the M.D. I take it in preparation for the Ph.D. you



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were a Clinical and Research Fellow in Pharmacology
at Montreal General and at McGill?

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A. Yes. I did that while I was
doing my Ph.D.

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Q. In 1973 you became a Fellow of
The Royal College of Physicians of Canada?

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A. Yes, I did.

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Q. You are a member of a number of
professional societies, including the American Society
for Clinical Pharmacology and Therapeutics and the
Canadian Society for Clinical Pharmacology?

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A. That is correct.

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Q. You are licensed to practise
medicine in Ontario, and formerly you were so
licensed in Quebec as I understand it?

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A. Yes, that is correct.

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Q. Since 1973 you have held
teaching appointments at the University of Toronto,
both in the Department of Pharmacology and in the
Department of Medicine?

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A. Yes, and in Paediatrics and
Clinical Biochemistry as well.

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Q. As of 1978 you have been a
member of the attending staff at The Hospital for
Sick Children?

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A. I am sorry, did you say 1978?

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Q. Yes.

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A. Yes, well I actually started

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in January of 1979, but I think the appointment was probably 1978.

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Q. And you also and have been since that time a senior scientist in the Research Institute at the Hospital?

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A. Yes, that is correct.

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Q. You have been the Secretary-

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Treasurer of the Canadian Society for Clinical Pharmacology?

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A. Yes.

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Q. And responsible for all the funds of that organization?

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A. Yes, indeed, and they are not plentiful, it is a small job.

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Q. And you are the President Elect and indeed you may now be the incumbent President of the Canadian Society for Clinical Investigation?

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A. Yes, I am the President Elect right now.

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Q. Doctor, you have published papers on a vast variety of pharmacological topics. I confess I see only one of your publications which

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expressly refers to the drug which particularly
concerns us, the paper which was published in the
Journal of, what is that, Cardiological Pharmacology?

A. Cardiovascular Pharmacology.

Q. Thank you. On Digoxin-Verapamil
Interaction. Other than that you have not published
on the subject of digoxin, but I take it ---

THE COMMISSIONER: What number is that,
Mr. Lamek?

MR. LAMEK: I am sorry?

THE COMMISSIONER: What number is
that on the list?

MR. LAMEK: It is No. 76 in the list
of publications, Mr. Commissioner.

THE WITNESS: No, digoxin has never
been a central research interest of mine.

MR. LAMEK: Q. I take it it has been
something of an interest of yours for the last two
and a half years?

A. It has been a little hard to
escape, yes.

Q. Doctor, I wonder if we could
mark a copy of the curriculum vitae that you provided
to me as the next exhibit?

THE COMMISSIONER: Yes.



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--- EXHIBIT NO. 253: Curriculum Vitae of
Dr. Stuart Maxwell McLeod.

MR. LAMEK: Q. Dr. MacLeod, as I
understand it you first became involved in the matters
that concern this Commission in mid-March of 1981,
and in particular I believe on March the 17th when
Dr. Costigan spoke to you?

A. Yes, that is correct.

Q. And he spoke to you, as I
understand it, about the digoxin levels that had been
reported on samples drawn from Kevin Pacsai?

A. Yes, that would be correct.

Q. I take it the information that
he had and that he brought to you, was that a level of
greater than 10 nanograms per millilitre had been
measured in ante mortem serum from that child; and
that a further level of 25 or 26 nanograms had been
reported from a post mortem sample from the child?

A. That would fit with my
recollections.

Q. Did you express any views to
Dr. Costigan at that time about the significance of
those levels?

A. Well, I think clearly we all,
everybody involved felt they were significant.



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Q. Yes.

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A. And we certainly discussed what might be done to further determine their significance.

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I recall that we specifically discussed the possibility of measuring tissue concentrations, I believe I provided him with a paper on the subject suggesting a method, and we had some further discussions about the possibility of medication error, or some error in manufacturing of the drug. We made arrangements to test the materials, the digoxin solutions that were available in the Hospital at the time. I am sure all this has come out previously.

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Q. Dr. MacLeod, are you focussing now on the events of March 17th when you had that first discussion?

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A. That is correct.

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Q. We have heard what Dr. Costigan did with that information and whatever information he had in his conversation with Dr. Carver on the following day.

Did you also discuss with him - I am sorry, did you also discuss at that time, that is to say March the 17th, with anyone else on the staff at the Hospital, the Pacsai digoxin levels?



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A. The 17th I believe was a
Tuesday, wasn't it?

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Q. Yes.

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A. I believe at some point I
discussed it. I would have had discussions with
Dr. Fowler, with Dr. Carver and with Dr. Soldin in
the Clinical Biochemistry Department.

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Q. I take it you can't recall
whether that was on the Tuesday or the Wednesday?

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A. No. It certainly wasn't the
Tuesday, the Tuesday was late in the afternoon I
believe and then this would have been on the Wednesday
and Thursday.

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Q. Between that initial conver-
sation with Dr. Costigan on as you have said the
Tuesday afternoon, and let us say by the end of say
the Friday of that week, which would be the 20th, do
you recall any further discussions, first with
Dr. Costigan?

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A. Not specifically. I am sure
that I had conversations with him about what was
in progress.

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Q. And you have said that you had
conversations with Drs. Carver and Fowler, can you
recall the content of those discussions?



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A. No, just about the extent of the problem and what could be done. Again, the same sort of thing, what was the likelihood of error, or error in manufacturing, error in administration, error in Hamilton versus error in Toronto, this sort of thing, but a very general discussion.

Q. Do you recall in that time period that is to say Tuesday to end of day on Friday, any discussions with any other physicians, or members of the staff at the Hospital?

A. Well, I probably had more specific discussions with Dr. Soldin, because we were interested to analyze materials, the paediatric digoxin solutions that were available on the ward.

Q. Yes.

A. And we had some discussions about finding the multi-dose bottle from which Pacsai had ostensibly been dosed, and we couldn't find that, it had been discarded. We then tested other bottles of digoxin elixir that were available in the Hospital and satisfied ourselves that there was no mistake in the formulation of those bottles. I am sure at the time we also contacted Burroughs Welcome who manufactured it and asked them if they had had any other problems. These were the sort of things that we did.



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Q. Doctor, did you learn on Saturday evening that another child, that is to say Allana Miller, had died that morning and it had been established she had a digoxin level in post mortem blood of 78 nanograms?

A. Yes, I heard that about 7 o'clock in the evening.

Q. Were you called at home?

A. Yes, I was called by Dr. Soldin this time. I believe there is a police note saying Costigan, but that is a mistake.

Q. And other than the information that came to you from Dr. Soldin in that conversation, do you recall anything else that was discussed between you at that time?

A. Yes. Well, in the course of that evening, that Saturday evening, there were a number of conversations that followed.

Q. With Soldin?

A. With Soldin and with Dr. Carver I believe, I probably spoke to each of them two or three times.

Q. You did not go to the Hospital that evening?

A. No.



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Q. What was the substance of those conversations?

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A. Well, we discussed at that time again how the possible scenarios that might account for a digoxin concentration of that magnitude. Dr. Carver and I discussed what might be done in the short run to make sure it didn't happen again.

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Q. Yes.

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A. And this led to the decision to lock up the digoxin in the Hospital, to place it in the narcotics cupboards on the various wards. Also the decision was made, as I guess you know, to do an inventory of what digoxin was available.

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Q. Are you able to tell me which were these scenarios that you discussed between you as possible explanations for this level; and would you also discuss at the same time this level and the Pacsai level?

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A. Well, it was very difficult to take them in isolation.

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Q. Yes.

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A. Clearly we were concerned about Pacsai, although the concentration in that instance was such that it might have been explained by error. I mean there obviously were a number of possibilities



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that we could consider.

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The level in the Miller case was of a different order of magnitude really. You have to understand a concentration like that comes across to somebody like myself, it shines out as being the highest level you have ever heard of, I mean outside of a suicidal overdose or something like this. So immediately the conclusion was that we were likely dealing with an intentional overdose and that was certainly the sentiments on the Saturday night.



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Q. Were you involved in any way in the implementation of the decisions made on Saturday night either to lockup digoxin or to conduct an inventory?

A. Well, I had discussed both of these measures with Dr. Carver and he implemented them. I was not in the Hospital. I think they were implemented - it is probably not correct to say an inventory on Saturday night. Certainly the decision was to place all the digoxin in the Hospital in the narcotic cupboard and put it under certain control procedures. I do not think the term inventory would have been used at that time. That really came up the next morning.

Q. We know in fact that an inventory of sorts was done on the Saturday night and then it was done again by a different person on the Sunday. Were you involved in any way in the inventory on Sunday?

A. I arranged that, actually. Because of my position I have a certain amount of responsibility for the pharmacy in the Hospital. I am the Chairman of the Pharmacy and Therapeutics Committee, and I spoke several times with the pharmacist who was on duty that day and arranged



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with her to have the inventory done.

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Q. Then you learned on Sunday,
March 22nd, I take it, of the death of Justin Cook?

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A. That is correct.

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Q. Can you tell me when and from
whom you got that information?

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A. That would - I'm not really
sure on time but it would have been 8:30 or 9 o'clock
in the morning, I believe. I think I was again called
by Dr. Soldin. I subsequently again had conversations
with a great variety of people over the next hour or
so, so I'm not sure who was first. It was either
Dr. Carver or Dr. Soldin.

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Q. Did you learn at that time
about the digoxin levels that had been registered on
assays of his blood samples?

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A. Yes, I did.

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Q. Did you understand that one
of those samples had been drawn during the course of
the resuscitation?

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A. Yes, I did.

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Q. And another sample at post
mortem?

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A. Yes.

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Q. You had discussions with



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Dr. Carver as well, you think, on the Sunday?

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A. Certainly. There was a kind
of a cascade, I think.

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Q. In the course of those
discussions, was the thinking that you have told me
about from the Saturday evening telephone conversations
advanced any further?

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A. I think that these events
tended to confirm our initial belief that there was
an intentional overdose, and obviously these were
magnified because of the fact that Cook was not
receiving digoxin, and there was a measurement done
on the intravenous solution which showed that there
was none in the intravenous bag, and that had come
out. I would say by that time on Sunday morning
most of us were quite convinced that there had been
intentional overdoses given.

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Q. Do you recall any discussions
on Sunday with any staff member of the Cardiology
Division?

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A. I certainly spoke to Dr. Rowe
and Dr. Fowler. I cannot remember if I spoke to
anybody else on that Sunday morning.

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Q. On the Sunday morning. What
was the content, in general terms, of those discussions?



MacLeod, dr.ex.
(Lamek)

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A. Again, just general discussions about what was going on, what should be done. I remember specifically discussing the question of the inventory probably with both of them, but specifically with Dr. Rowe, because it became apparent with the pharmacy inventory that there were places in the Hospital where digoxin could be found that had not been uncovered by Dr. Costigan and some of the wards did not for instance want to give up the digoxin on their crash carts, some sort of primordial connection. So I had some discussion with Dr. Rowe as to whether or not he thought it was reasonable by administrative fiat to remove this and he felt it was and we eventually did.

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Q. Do you recall any discussions with Dr. Rowe or any other member of the Cardiology Division on the Sunday, March 22nd, of the kind that you have told me about with Dr. Carver, that is to say thoughts as to how these deaths could have occurred with these digoxin levels?

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A. I don't think that any of us discussed it very specifically, to be honest with you. I think what I have told you is true, that we all accepted that this is probably what had happened.

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Q. Dr. MacLeod, I am aware that



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on Monday, March 23rd, and on certain occasions there-
after you attended meetings at which coroners and
police may have been present, and we may have to
hear from you later about those meetings.

Have you at some time since that third
week of March, 1981, reviewed the Hospital records
of Justin Cook, Allana Miller, Kevin Pacsai and
Janice Estrella?

A. I have reviewed - I must say
I never saw the records between that time and the
time after the preliminary hearing but since that
time I have had a chance to look at all of those
records in some depth or other. I really have not
been through, with a fine tooth comb, any of the
records.

Q. I take it from that answer
that you had not, prior to March 22, looked at the
charts of any of those children?

A. No, I don't believe I had seen
any of them or written in them.

Q. And have you also at some time
reviewed, although not perhaps in great detail, the
medical charts of Jordan Hines, Stephanie Lombardo
and Jesse Belanger?

A. I have seen all those charts.



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Q. And again that I take it is since the end of the preliminary in May of 1982?

A. All of this since mid-June of 1982.

Q. You gave evidence at that preliminary hearing, did you not, Dr. MacLeod?

A. Yes, I did.

Q. And at that time you gave some evidence about digoxin, also some with respect to individual cases, but I would like if I may, it may be the shortest way of doing it, to review some of the general evidence and ask you if your views have changed in any of these respects in the past 18 months. The evidence is found, Mr. Commissioner, in Volume 22 of the preliminary hearing transcript. At page 33 of that transcript you were asked, Dr. MacLeod, beginning at line 24, Mr. Commissioner:

"...if one had received a large dose of digoxin, a toxic dose of digoxin, would that have an effect on the potassium level of the child?"

You answered, yes, it would.

Q. What would it do to the potassium level?

A. It would normally increase



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"the serum potassium. Digoxin affects the kidney's ability to remove potassium so potassium generally rises."

Again, on page 34, in the context of potassium the question was asked at line 4:

"Q. If potassium were high, were going up, and efforts are made to reduce the potassium level what would that do to the toxic dose of digoxin that may have been in the baby's system?"

A. Well, it might change its distribution. It might change. It is felt that potassium/digoxin in some way compete for binding in the heart so if potassium goes down the amount of digoxin in the heart might go up slightly, but this would not really be a significant change, to my mind."

Based upon the knowledge that you have and the literature you have now read are those still your views with respect to the potassium/digoxin question?

A. Yes. Certainly the first view is unchanged. There's no question, digoxin can cause increases in potassium. As to whether or not the



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changes in potassium, the lowering of potassium might in some way increase the tissue binding of digoxin, I think I might view that - I think you quoted me as saying it was not likely to be significant. I think now I might say it could be significant under some circumstances, but basically the response is the same.

Q. It is important to us, and proper in any event, Doctor, to go to the other side of the question that was asked. You said that a toxic dose of digoxin would normally increase the serum potassium and we have heard that also elevated potassium may have the effect of increasing the serum digoxin. Is that also your understanding?

A. Yes, that is correct.

Q. In any given situation where you see it one and the same time elevated serum digoxin and elevated serum potassium, is it possible to differentiate which is the cause and which is the effect?

A. Not without more information. If you just take an isolated point and say at this moment digoxin is high, and potassium is high, I don't think you can make any inferences about which came first.



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Q. You were sitting here this morning, I understand, when Dr. Bain was giving his evidence and I was asking him the questions about elevated potassium in Kevin Pacsai, at the same time as we know there was elevated digoxin.

A. I heard the discussion. I could not answer, either. He said I could, but I could not.

Q. It really is a chicken and egg situation there, is it not? If that is all you know, the elevated level of each, it is difficult to ascribe the elevation of one to the other.

A. It is much like the problem we have with all of this analytical data that when you take a measurement at an isolated point it is very hard to extrapolate backwards.

Q. You were also asked in cross-examination, Doctor, about the doses that would have to be administered to an infant to achieve certain serum concentrations, and I am going to be more interested in your current views on that of course because we have been hearing some of the information from Dr. Spielberg about that so I will not ask you about your evidence at the preliminary in detail on that, but there were a couple of specific questions. They are found at page 44, Mr. Commissioner, Volume 22 beginning at line 18 and going over to line 8 on the following page.



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You were asked these questions,
Dr. MacLeod:
"Q. Let's assume that a child with
a 4 kilogram weight was given 2 ccs
of the adult intravenous solution or
the intravenous digoxin, how soon after
administration directly into a tube
(and I assume IV tube) could one expect
that child to die or can one say?"

And your answer was:

"A. You can't say with any certainty
but within an hour or two unless some-
thing was done to intervene".

And then you said, you know, there are
sorts of anomalous things in the literature.

THE COMMISSIONER: I'm sorry, what
was the dosage again?

MR. LAMEK: 2 ccs of the adult
preparation.

A. So, 500 micrograms.

THE COMMISSIONER: That doesn't
help me. How is that in relation to a vial?

THE WITNESS: That is one adult
ampule.

MR. LAMEK: Q. And you say that



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2 subject to the anomaly cases you can find all over
3 the place you would expect death to occur in that
4 child within an hour or two unless something was
5 done to intervene. And you went on on page 45:

2
6 "Certainly there is a lag period
7 during which it enters the heart and
8 begins to have its pharmacological
9 effect. Its peak effect would come,
10 you begin to see effects, say, after
11 an intravenous dose within 15 minutes,
12 15 or 20 minutes and you would see
13 peak effects probably between one and
two hours."

14 Now, Doctor, are those still your
15 views with respect to the kind of timing one might
16 normally expect to see with that sort of dose given
to that sort of child?

17 A. Well, I think those views
18 are unchanged with respect to that hypothetical dose
19 that you have named?

20 Q. Yes.

21 A. It probably should be
22 qualified or should have been qualified at that time
23 to say that if a much higher dose is given then almost
24 anything becomes possible I think in terms of time
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of onset. So, I think if we were talking, say,
three adult ampules instead of one then you might
reasonably expect to see some pharmacological effect
within seconds or minutes.

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Q. Yes.

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A. However, if you are talking
one adult vial given in that fashion then I think
that probably the times I used on that occasion were
correct.

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Q. Thank you. You were then

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asked about the post mortem phenomenon, the sort
of multiplier effect, the changes in serum levels
that occur after death and that is found, Mr.

12

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Commissioner, on page 48 of Volume 22 beginning at
line 3. You were asked these questions, Doctor,
and gave these answers:

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"Q. Doctor, after the drug digoxin
is administered would the distribution
of it in the body change after death?

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A. It might change a little
bit, I wouldn't expect it to change
very substantially."

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Now, let me pause there. Is that
still your view?

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A. Yes, that is correct.

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Q. By distribution did you understand the question to be referring to distribution between different tissues or between tissue and blood?

A. Between tissue and blood.

Q. Okay.

A. Oh, no, I am sorry, between -- we are into a problem here because we are really talking about half of one per cent of the total body mode of digoxin.

Q. That's right.

A. That is in the circulation.

Q. The bath tub thimble situation?

A. You know, I wouldn't expect massive shifts. I mean, you don't have digoxin moving from liver to heart after death.

Q. Yes.

A. However, a very small shift may result in what seemed to be quite substantial changes in blood concentration.

Q. Right, okay.

A. So, it may have been misleading what I said there before.

Q. Okay. I think it is



1
2 important to have that explanation given to it?

3 A. Yes.

5 4 Q. The question went on, sir:
5 "If a post mortem is done, say, some
6 hours after death, would one expect
7 that the digoxin level taken at post
8 mortem would be different than what
9 it might have been when the baby
10 actually died?

11 A. Well, I mean, there are
12 two phenomena that might occur; one,
13 if there is a certain amount of
14 digoxin distributed into muscle and
15 the heart some of that may come back
16 out of that muscle and into the fluid
17 adjacent to the muscle, which is blood,
18 or may be blood in the cavity of the
19 heart. So, there may be an increase
20 in level from that phenomenon. If
21 there was a post mortem sample that
22 was taken, say, some hours after an
23 intravenous dose there may in the
24 immediate post mortem be some dis-
25 tribution out of the blood into the
adjacent tissues, so, the value might



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2 "go down a little bit in the post
3 mortem period. So, really, either
4 type of error is possible but I
5 wouldn't expect shifts of this kind
6 to be a very important factor in
7 interpreting these types of
8 concentrations we've been talking of."
9 Did those answers represent your
10 current use?

11 A. Yes, they do.

12 Q. I suppose, depending upon
13 the relative concentrations in serum and tissue,
14 even post mortem it is possible to contemplate that
15 the transfer may continue to be from blood to tissue?

16 A. Yes. Well, the second
17 situation that I was describing there I was really
18 thinking again in hypothetical terms of a very high
19 serum concentration.

20 Q. Yes.

21 A. Of the order of 75 or 100
22 nanograms per ml, something which is taken clearly
23 during the, I guess you are conversant with the
24 trends alpha phase or distribution phase.

25 Q. Yes.

A. I mean, there might be still



1
2 some movement as part of that distribution from
3 blood into tissue even occurring in the immediate
4 post mortem period. I think that would only happen
5 if you had a very high concentration in blood at the
6 time of death.

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8 Q. But by very high concentration
9 you have just suggested something of the order of
10 75 or 100?

11 A. That is the order I'm
12 talking about.

13 Q. Well, let me understand
14 that clearly, Doctor. We have heard really about the
15 multiplier effect in blood which presupposes that
16 the blood level goes up or, indeed, it says it goes
17 up. We have understood that that is not something
18 that uniformly occurs or occurs at any predictable
19 rate of multiplication?

20 A. That's correct.

21 Q. Are you suggesting that it
22 may also be the case in children such as some of
23 those that we are dealing with here that a post
24 mortem level may be less than an ante mortem level?

25 A. Yes. Again, in the very
high ones. All I am suggesting is that there is
probably a tendency to establish an equilibrium



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2 between the tissue and the adjacent blood so that
3 if the concentration in tissue, for example, is
4 50 nanograms per gram of tissue and in the adjacent
5 blood is 10 then there might be tendency for move-
6 ment -- I am sorry, I am confusing you, I am wrong.
7 If the concentration of blood is 50 and it is 10 in
8 tissue there might be a tendency for movement from
9 blood into the adjacent tissue. I don't know whether
10 that occurs. To my knowledge it has not been studied,
11 it would really be only of limited interest
12 forensically but I don't think it is an important
13 point. I believe it is probably true though.

8
13 Q. Okay. Finally, Dr. MacLeod,
14 you were asked again about the time that it might
15 take to reach peak effect. This was in re-examination
16 of you at page 48, sir, beginning at line 27 and
17 going over to the next page.

17 You were asked:

18 "Q. Now, the types of concentrations
19 that we are dealing with here range
20 from 25 nanograms to about 100
21 nanograms after death."

22 You indicated to Mr. Cooper something
23 about the time effect with respect to death with
24 amounts of that calibre:
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MacLeod, dr.ex.
(Lamek)

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"Would that time factor vary as to
how the drug was administered, whether
orally or by intravenous injection."
And you said, oh yes, you would expect a peak effect
to come more rapidly after an intravenous injection.
I take it that's still your view today?

A. That is still my view.

Q. "Q. Can you say how rapid
it would be?

A. The peak effect?

Q. Yes.

A. I would expect it to occur
within two hours.

Q. You are referring to when
would the first signs of the drug,
supposing it was administered intra-
venously with amounts this high, when
would you expect the first signs of
trouble to occur?

A. I think if the patient was
being closely observed I think there
would be signs visible within 15 to
30 minutes of the administration.

Q. What signs would those be?

A. Changes in the



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"electrocardiogram, possibly changes in the pulse, this sort of thing, early cardiac changes. These would become more pronounced as time went on and would peak at one and a half to two hours.

Q. All right. And the peak, would that be when the death would occur?

A. That's what one would anticipate."

I ask you, Doctor, are those still your views with respect to the time one might see the onset of symptoms and that of peak?

A. Well, I would qualify it a little bit. There is really quite an extensive body of literature on the time of onset of dig. effect, digoxin effects when digoxin is given in therapeutic doses intravenously for the treatment of certain kinds of cardiac rhythm disturbances. Normally you don't expect to see onset of the effect until about 15 minutes. It varies a little bit between different preparations of digitalis and there are others that are used, but, say, 15 minutes would be an average here and then the peak effect



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maybe occurs at two hours, as late as two hours.

Now, the qualifier is that, again, clearly, if you use a very large dose of digoxin, many times the therapeutic dose, even though you may only see 5 per cent of the effect at 15 minutes or 5 minutes, you may nonetheless see a significant pharmacologic effect and certainly death from that cause might ensue any time after the onset of pharmacologic effect. You might never get to the peak effect.

Q. You mean the recipient may succumb long before there's been total absorption of the drug?

A. Well, no, it is not a question of absorption.

Q. Distribution of the drug?

A. Distribution, yes.

Q. Yes.

A. That is what I am suggesting. So, I think that that reply was okay as far as it went but it was pretty simple, pretty well simplified and there really is a range of possibility that we didn't discuss there.

Q. And then with respect to oral administration it was suggested on page 51 that



1
2 you would expect the first effect to be pretty
3 subtle and not really clinically detectable but
4 with the kinds of doses that we are presumably
5 talking about you said you should start to see
6 effects that may be one and a half to two hours and
7 the peak effect would follow by a couple of hours
8 at the end of the administration of the drug?

12
9 A. This again should be
10 qualified to referring to normal therapeutic doses
11 or even slightly super normal therapeutic doses
12 but doesn't necessarily apply to toxic overdoses.

13 Q. But I take it even with
14 respect to toxic overdoses there will be a longer
15 lag before the first manifestation of symptoms of
16 toxicity than in the case of intravenous administra-
17 tion?

18 A. Oh, clearly, there has to
19 be a lag for absorption to occur before anything
20 happens.,

21 Q. Yes.

22 A. Yes.

23 THE COMMISSIONER: What was the peak?

24 MR. LAMEK: A couple of hours after
25 the end of the administration. I think you were
contemplating at that stage an ongoing administration,



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were you not, orally?

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A. No.

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Q. Was that absorption?

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A. I believe it was in response

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to a hypothetical question in which dose really
wasn't specified. I mean, that entire discussion

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was very general and unpremeditated to be able to
appreciate it to read it closely.

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Q. The question, to be totally

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clear about it was:

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"Can you give us any estimate as to
the outside range of the effect of the
drug, the first signs of the effect
of the drug if it were administered
through a nasal gastric tube".

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And you say: "If it were dripping in slowly, yes,
with the tube in the food feeding."

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A. Yes. So, it probably would

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still apply as an outside range as the question was
put.

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Q. Now, can we come, Dr.

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MacLeod, to some of the particular matters that
concern us and some of them ---

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THE COMMISSIONER: I wonder if I
could just pause.

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MR. LAMEK: Yes.

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2 THE COMMISSIONER: If we look at
3 Exhibit 217. Do we have Exhibit 217? What I am
4 concerned about, you gave the figure of two hours
5 for the peak and that hadn't been what I had
6 understood.

7 THE WITNESS: We are talking about
8 peak effect not peak serum concentration.

9 THE COMMISSIONER: Not the peak
10 amount of the serum.

11 THE WITNESS: No, they don't corres-
12 pond at all.

13 THE COMMISSIONER: Oh, I see, all
14 right.

15 MR. LAMEK: Indeed they are at
16 entirely the opposite end of the alpha phase of
17 the curve, are they not?

18 THE COMMISSIONER: The peak effect of
19 course, yes, because there is no affect on the blood
20 at all, it gets into the tissue.

21 THE WITNESS: Yes. Well, that is one
22 of the reasons why there is a lag but there is a
23 chain of biochemical events that has to take place
24 before you see the pharmacologic effects. So, there
25 is really very little relationship between the
concentration in blood of those effects.



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THE COMMISSIONER: Yes. Yes, Mr.

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Olah.

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MR. OLAH: Excuse me, Mr. Commissioner,

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I wonder if my friend could assist us in perhaps

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defining the phrase the Doctor used when he said a

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couple of hours. It becomes pretty critical to some
of our clients.

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THE COMMISSIONER: You mean what he

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meant by a couple of hours?

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MR. OLAH: Yes.

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THE COMMISSIONER: Well, it is

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usually two, isn't it?

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MR. OLAH: That's what I would have

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thought but he talked about the first effects would

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be one and a half to two hours and the peak effect

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in a couple of hours, presumably some time after

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THE COMMISSIONER: Are we talking

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about the oral administration?

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MR. OLAH: That's correct.

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MR. LAMEK: That wasn't quite the

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answer but by all means let us clarify what a

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couple means. The answer - I think I have it.

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MR. OLAH: It is at page 51.

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MR. LAMEK: Page 51 where you said,

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Dr. MacLeod that:

"...I would expect the first effects to be pretty subtle and really not clinically detectable."

And you would start to see those effects at maybe one and a half or two hours and the peak effect would follow by a couple of hours the end of the administration of the drug.

Now, first, by a couple do you mean two or so and if so what does so mean?

A. Yes, well, I think it is very unclear. It reflects the general way in which the question was asked. I think, you know, you cannot give specific answers to a hypothetical question that doesn't specify dose or formulation that is being used. But what I was saying was that after an oral administration of digoxin there is a time when you are going to see nothing because the drug has to be absorbed and how fast it is absorbed will depend on the formulation that is used and may depend upon the condition of the recipient and many other things, presence of food.

Eventually it is absorbed and at that point you then have this lag that is required for the biochemical effect of digoxin, the same sort of



1
2 thing you see with intravenous administration.

17 3 There has to be time for the drug to bind to sodium
4 potassium ATPase, that I guess you have heard about,
5 and then to exert its effects on the heart or other
6 tissues.

7 Beyond that, there is a further lag
8 between the time when you could first measure those
9 effects and when you could measure them would really
10 depend on how closely you are looking. If you are
11 a clinical cardiologist in an intensive care unit
12 you might not have the tools immediately at hand to
13 see the effect. If you are doing a pharmacology
14 experiment under control circumstances with normal
15 volunteers you might see it very soon. But that
16 is what I was referring to with the subtleties but
17 at some point it becomes evident that there is a
18 pharmacologic effect and beyond that there is a
19 further lag until you see the peak effect and that
20 lag, I think it is very unclear in my testimony of
21 two years ago, but that lag would probably be a
22 further two hours, but again, that would depend very
23 much on the absolute dose that was given and what
24 formulation was used.

25 So, it is really such a generalization
that it is not worth very much.



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Q. As I understood the question to you in that case, Dr. MacLeod, you were asked to contemplate an ongoing slow oral administration?

A. That is correct.

Q. And I understood your answer to be that even while the dose were being administered in that way you might begin to see the first effects, but the peak would occur a couple, two hours after the completion of the dose?

A. Yes, you are absolutely correct. I think the hypothesis there was that it had been added to the tube feeding and was going in gradually over a period of time. So this would prolong this process even further, and the two hours, the couple of hours which certainly means two, would be the time beyond the end of the last administration. So the time when the tube feeding finished and there was no more digoxin entering the stomach your peak effect would probably come about two hours after that, bearing in mind that you have a cumulative absorption and really a cumulative dose of digoxin being given, but still too hypothetical for my taste.

Q. Let us turn please to the child Justin Cook. You have already said this morning, Doctor, and you are obviously aware that



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2 digoxin had not been prescribed for that child. You
3 are aware of the digoxin levels that were measured
4 in that child. The evidence has been that in blood
5 drawn 10 minutes into the resuscitation procedure,
6 a level of 72 nanograms was recorded; and blood drawn
7 after the child had been declared dead, an hour after
8 death, a level of 68 nanograms was recorded; and
9 another post mortem sample, a level of greater than
10 100; and heart blood drawn at autopsy, a level of 91;
11 in fresh heart tissue a level of 1177 nanograms; and
12 in fresh lung tissue a level of 153. Of course there
13 were many other readings in fixed tissues, and we
14 have these readings in blood and in fresh tissue.

15 Doctor, is it your belief, or opinion,
16 that one can properly infer in the light of those
17 readings that digoxin was administered to this baby?

18 A. Yes, I think that is --

19 Q. Is there any other plausible
20 explanation for those levels?

21 A. Not in my opinion.

22 Q. Do you have an opinion as to
23 whether the baby's death was caused by digoxin
24 intoxication?

25 A. I think that is really impossible
to tell. That is a difficulty with many of these



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cases that you have been discussing. Clearly there is a high concentration of digoxin at the time of death. Whether that causes death or not is another question. In fact, the actual mode of death with digoxin is so relatively non-specific that it becomes impossible to say, certainly in Cook's case and certainly in several of the others.

Q. Impossible to say with any absolute certainty. Do you have a view as to the likelihood of digoxin intoxication having caused this child's death?

A. No, I think in the case of Cook I couldn't even go that far, I think you can flip a coin.

I mean, this was a child who had significant heart disease and was certainly a candidate for sudden death. The fact that there was digoxin there at the time of death certainly is suggestive, but that is really the only evidence in favour of digoxin overdose being the cause of death. And you know, to my mind, that one fact is not sufficient evidence to call that the cause of death.

Q. What more would you need?

A. You would have to have some knowledge of the time of the administration of the



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digoxin, and where you were on the time concentration curve, and probably serial electrocardiograms showing the changes that had occurred in relationship to the change in concentration. Of course it would be a heck of a lot easier if you had a recipient who didn't have any other likely cause for sudden death.

I mean, digoxin, death from digoxin overdose is - or digoxin toxicity - is generally a diagnosis of exclusion. You know, it is a common medical term, but when you have ruled out all the other possibilities then it becomes very easy to accept digoxin or other drug toxicity as the cause of death. Here you can't rule out the other causes, at least I can't, to my satisfaction.

Q. Doctor, I must confess I am having some difficulty with that. Are you aware of any other tests in the reported literature at least, or in your own experience, where fresh tissue concentrations of the order of those measured in Justin Cook have been measured in a patient who was not considered to have died of digoxin intoxication?

A. Well, the qualifier in there maybe is fresh. There certainly are figures of that sort in tissues, well, I guess they are fresh tissues now that I think of it. So, yes, there are certainly



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cases - there is for instance measurements of digoxin in right atrial appendage of children going to cardiac surgery, are of that order, they are not quite 1100, but 850 say. I mean, I don't think that is a highly significant difference of that level.

Q. Were they also accompanied by levels of 72 nanograms in serum?

A. At some point, probably.

Q. Were they co-existent?

A. Well, see that is tricky, because you don't, you wouldn't normally take a serum digoxin measurement at that time. The difficulty here again is knowing the timing between administration and when that sample was taken. We don't know if it was taken five seconds after the dosage was given, or five minutes, or fifty minutes.

Q. Do we not, Doctor?

A. So if we don't know that then we have trouble.

Q. We can eliminate five seconds, can we not?

A. Probably, yes, I will give you that, you know it's not ---

Q. I would have thought you might, Doctor.



K.6

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A. I can argue it.

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Q. Unless you are prepared to

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posit more than one unprescribed dose of digoxin to
this child you have to account somehow for the tissue
concentrations, do you not?

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(2)

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A. You do, and this is one major

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gap in our knowledge, and that is the rate at which

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the drug distributes into the tissue, myocardium in

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this case, after an acute dose of digoxin. We really

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don't know that and probably never will because it

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is not a study that you can do.

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So I mean what we have are fragments

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of information about tissue concentrations of digoxin

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that are taken at variable times after administration,

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maybe hours, maybe after death. But we don't have

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samples that have been taken 5 seconds, 50 seconds

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or 5 minutes after digoxin administration by the

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intravenous route and that is why there is an element

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of doubt. I agree with you 99.9 per cent certainly

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five seconds is not enough. There are lots of

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examples in pharmacology of drugs disappearing into

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tissues within the first circulation through the

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tissue and circulation time is 15 seconds.

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Q. We know from your own practice

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and procedures in the Hospital, Doctor, that that is



K.7

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likely not the case with digoxin, is it, because you are concerned that samples not be drawn within close temporal proximity to the administration?

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A. No, that is a question of avoiding the alpha phase, the distribution phase which is misleading in terms of serum concentrations. What we don't know in any way is what happens to tissue concentrations during that alpha phase.

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Q. Forgive me, I must be very simple minded about this; if the digoxin is not in blood and it is not in tissue, where is it hiding?

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A. Oh, no, it may be in tissue, I mean it is not in blood, that we know.

13

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Q. Yes.

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A. Or it is disappearing from blood, very rapidly, that is what the alpha phase is.

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Now, what we don't know is where it is going. I mean there has to be a converse to that alpha phase and I am sure you have had lots of time concentration curves drawn for you?

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Q. Yes.

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A. And it is coming down very fast, a half life of 15 minutes and it is disappearing into tissues.

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Now, one can assume that it is going

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equally into liver, kidney, red blood cells, myocardium,
skeletal muscle.

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Q. Yes.

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A. It may not be. Maybe it goes
initially into the myocardium, maybe it is all sitting
in the myocardium. There is certainly some evidence
from Cook data that there is a lot more in the
myocardium than there was in the lung, for example.

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Q. Yes.

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A. And in other tissues I guess,
you have just read out the numbers.

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THE COMMISSIONER: I think part of the
problem was it sounded from your answer as though
the digoxin somehow or other was disappearing from
the body entirely. That is not what you meant?

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THE WITNESS: Oh no, it is going into
tissue.

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THE COMMISSIONER: You just don't
know the rate it goes into particular tissue?

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THE WITNESS: That is exactly correct,
I am sorry I didn't mean to suggest it was disappearing
from the body.

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THE COMMISSIONER: We know the rate
that it leaves because that is what the alpha phase is.

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THE WITNESS: We know the rate it
leaves the blood.

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K.9

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THE COMMISSIONER: Yes.

THE WITNESS: We know the rate at which it disappears from the blood compartment.

THE COMMISSIONER: That it is going into tissue, some tissue, somewhere.

THE WITNESS: And we know really it is going into many tissues, but we don't know the actual details of the pattern of that distribution. So I mean, I am just being the devil's advocate, but it is possible within a minute after an intravenous dose of digoxin that you have a very high concentration in myocardium, maybe if you wait 10 minutes you have a lower concentration.

THE COMMISSIONER: And a higher concentration in other tissues?

THE WITNESS: Yes, in some other tissues.

THE COMMISSIONER: That is possible?

THE WITNESS: I am sorry?

THE COMMISSIONER: I was just going to ask why you used the word "acute administration"? I know that is a heavy dose but does it make any difference in the alpha phase whether it is acute or not?

THE WITNESS: Well, there are a number



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of things that may make a difference. There is clearly evidence that the pattern of distribution is likely to be different with ongoing administrations, or somebody who has been taking digoxin for a month.

THE COMMISSIONER: Oh, yes.

THE WITNESS: Or by mouth, orally, tablets once or twice a day. I mean, that is going to give you a different pattern from an acute intravenous administration of the drug. We have data on tissue distribution, but most of it comes from chronic dosing, that is long-term dosing.

THE COMMISSIONER: A person who has had digoxin, let us say for a matter of days, or weeks --

THE WITNESS: Yes.

THE COMMISSIONER: -- he is digitalized, he receives his normal therapeutic dose in one example, and in another one he receives a massive overdose, will there be any difference in the curve?

THE WITNESS: There may well be, I don't think that is known. There certainly is going to be a difference in the curve, in the shape of the curve between somebody who has never had digoxin before.

THE COMMISSIONER: We are taking this person ---



K.11

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THE WITNESS: Yes.

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THE COMMISSIONER: One person, and

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whether he gets a regular therapeutic dose --

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THE WITNESS: Yes.

6

THE COMMISSIONER: -- or a massive
overdose. I had understood this curve was invariable?

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THE WITNESS: Well it is variable.

8

THE COMMISSIONER: No, I said

9

invariable.

10

THE WITNESS: Oh, invariable, no, I

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don't - I think there is ---

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THE COMMISSIONER: The half life will

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change?

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THE WITNESS: The half life - I don't

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want to mislead you. There is some suggestion with
normal people, normal volunteers, that the shape of

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the curve is not dependent on dose. So this is after

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intravenous dosing, that you get exactly the same

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curve whether it is half a milligram, one milligram

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or one and a half milligrams that you give. There

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may well be a difference depending on whether or not

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the intravenously dosed is superimposed on a background
of chronic dosing with digoxin, or not. The idea

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being that there are a certain number of places in

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the body where digoxin can be bound, either specifically

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K.12

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or non-specifically, and that is another argument. If a large proportion of those binding sites are saturated, are already occupied by digoxin molecules then the behaviour of the new dose that is added on may be quite different from the behaviour of that same dose given to somebody who has never had digoxin before. All I am really saying is the tenth dose doesn't behave the same as the first dose.

THE COMMISSIONER: I don't really care too much, I care a little bit about that, but I care considerably about the fact that you say the acute dose is different, because that wasn't what I had understood and perhaps I should have understood that.

THE WITNESS: Well, we have -- I'm sorry.

THE COMMISSIONER: Because we had this curve presented to us. You say that you don't, or do you say that it will be different?

THE WITNESS: No, what I am really saying is we have no data on the behaviour of an acute dose of digoxin with respect to its distribution into tissue, we have lots of data on its behaviour in blood.

THE COMMISSIONER: We have no real



K.13

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data on any kind of distribution of - whether it is therapeutic or acute, or anything else, we have no data as to how it gets into the tissue, how it gets into which particular tissue?

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THE WITNESS: No.

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THE COMMISSIONER: You have told me that it may be different, an acute dose may have a different curve, and it may be longer than or shorter in the alpha phase, do you know which it is?

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THE WITNESS: No, I can't say, but it is likely to be different and this is the experience with many drugs. In fact drugs are usually studied pharmacokinetically both in an acute dosing situation and in a chronic dosing situation because they differ.

15

THE COMMISSIONER: Yes, do you think it is because of the saturation aspect?

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THE WITNESS: With digoxin I would think that is the most likely, this is purely theoretical and really this is not a question that could ever be answered in man, you could certainly do animal studies to answer this but you could never, you can't take serial biopsies from the heart, it is a little tough.

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That is why I am being the devil's advocate with respect to Cook's tissue concentration.



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I believe as you do that it does mean that there was a certain period of time elapsed between administration, but I don't know how much time was required for that concentration to be achievable.

Q. Certainly I want to get into the question of time and dose and I will do that after lunch. Let me just understand what you have told me so far, Dr. MacLeod. Do you regard it as probable that digoxin intoxication caused the death of Justin Cook?

A. Yes, I think it is probable.

Q. I didn't think we could be as far apart as we appeared to be actually.



L/DP/ak

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A. No, but I have to emphasize
that --

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Q. Of course.

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A. That you are going on one
piece of information which is the serum and tissue
concentrations. You really have no other evidence
to support that. I used my phrase post hoc ergo
propter hoc with Miss Cronk and
and I think that is a problem with all of these
cases. You cannot just assume because the level
was high that that means it was the cause of death.

12

Q. I recognize that.

13

14

A. In Cook I think it is likely,
but there is a balance.

15

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MR. LAMEK: Can we come back to
the time and dose after the lunch break?

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THE COMMISSIONER: Yes, all right.
2:30 then.

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MR. LAMEK: Thank you.

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MS. KITELY: Mr. Commissioner,
before we rise for the afternoon, might I mention
two things. First of all, I don't know how quickly
my friend intends to progress with the Doctor but
I would expect to cross-examine him and I cannot be
here this afternoon.



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THE COMMISSIONER: No. We had a private, improper conversation on the way from here to the Court House and Miss Kately told me all about that and I practically promised her that she would not have to cross-examine until tomorrow morning. Is there going to be any problem about that? I don't think so.

MS. KATELY: Unless my friends are also fast and Dr. MacLeod is released today.

THE COMMISSIONER: It has not been our past experience.

MS. KATELY: I thought I was reasonably safe, given the hour of starting.

The other thing, sir, is that just before the morning break Mr. Roland made a comment, and I took the liberty of actually listening to the tape before bringing it to the Court's attention. Quite frankly, I was concerned that an impression was left that it is only nurses, and, latterly, as my friend added, it may be residents who make medication errors. I just would not want that impression to be left before the Court. Am I safe in saying that my friend did not intend to leave that impression?

MR. ROLAND: No, it is whoever is there treating the patients and drawing up the drugs,



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(Lamek)

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and that includes doctors and nurses.

MS. KITELY: Thank you, sir.

THE COMMISSIONER: Yes, all right.

2:30.

---Luncheon recess.



AA/DP/ak

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2 ---Upon resuming at 2:30 p.m.

3 THE COMMISSIONER: This is not
4 entirely for Miss Kitley's benefit, but I forgot
5 to say this morning that the Court of Appeal, of
6 which I am still theoretically a member, is having a
7 meeting at 4 o'clock today, so I would like to
8 rise at 10 to 4:00, until 10 o'clock tomorrow morning.
9 So there we are.

10 Mr. Lamek.

11 MR. LAMEK: Thank you, sir.

12 Q. Dr. MacLeod, you were talking
13 to the Commissioner shortly before the lunch break
14 today about the different distribution curves that
15 you may find at different dosage levels and I under-
16 stand you have produced over the course of the lunch
17 break a copy of a paper published in the American
18 Heart Journal in 1978, I believe, October 1978
entitled "Dose Independent Pharmacokinetics of
Digoxin in Humans".

19 A. Yes, I have a copy.

20 Q. That may be of some assistance
21 to us in understanding the point you were making.

22 A. No, actually this does not
23 relate to the point I was making at all, but it does
24 illustrate some of the variability.
25



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2 I was making a completely
3 different point relating to the acute versus chronic
4 dosing, the distribution of the first dose as opposed
5 to the distribution of the 10th dose or the 20th
6 dose.

7 Q. There is however a Figure 1
8 which appears to show rather different shaped curves.

9 A. Actually not. They are clearly
10 different in concentration but that reflects the
11 difference in dose so the curves are in proportion
12 to the dose. This particular paper I brought forward
13 for a completely different point which you have not
14 raised yet, but if you want to get into it --

14 Q. You are interested in the
15 table on page 509, I take it?

16 A. That is correct. The figure
17 on page 509.

18 MR. LAMEK: In anticipation of
19 its becoming helpful at that stage, Doctor, maybe
20 we could mark it as an exhibit.

21 THE COMMISSIONER: Exhibit 254.

22 ---EXHIBIT NO. 254: Document entitled: "Dose
23 Independent Pharmacokinetics of Digoxin in Humans",
24 American Heart Journal,
25 October, 1978.



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2 MR. LAMEK: Q. I will put that away
3 for future use, next year.

4 I think as we arrived at the lunch
5 break, Doctor, you told me that you regarded it as
6 probable that digoxin intoxication was the cause of
7 Justin Cook's death.

8 A. I had told you before that I
9 thought it was a 50/50 chance, and I'm willing to
10 revise that to maybe 60/40. It is certainly possible,
11 with some degree of probability.

12 Q. And you arrived at that
13 conclusion in light of (a) the fact that the child
14 was not supposed to be on the drug at all and (b) that
15 indeed the cardiological evidence appears to be
16 that the drug was contra-indicated for him and
17 (c) the serum levels both before and after the
18 pronouncement of death and (d) the levels in fresh
19 heart and lung tissue.

20 A. With all respect, I don't think
21 the first two points have any relevance to a judgment
22 as to whether or not it was the cause of death.
23 Clearly he should not have received digoxin. I can
24 accept that. Clearly he did. Whether or not that
25 caused his death is something that can only be
proven by, say, a continuous electrocardiographic



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2 record or some very specific indication of digitalis
3 toxicity which we don't have.

4 The only objective finding which we
5 have in Cook, I believe, is serum and tissue concentra-
6 tions of digoxin. Clearly, that is enough to make
7 some sort of a presumptive decision that it likely
8 contributed to his death but whether it was the
9 ultimate cause of his death I cannot say with
any certainty.

10 Q. Does the fact of the drugs
11 having been contra-indicated have any significance,
12 in your view?

13 A. It certainly increases the
14 likelihood that the drug would have killed him had
15 it been given to him in overdose but again I do
16 not think it allows you to make any specific judgment
17 in this case. I think this is a little bit analogous
18 to the cause célèbre in Edmonton with the baby
19 that has been given the morphine, was given the
20 morphine in overdose, who subsequently died. The
21 question really becomes one of whether or not the
22 baby was going to die before the morphine had a
23 chance to act, not whether the morphine might have
24 caused death.

25 Q. In arriving at your conclusion,



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2 Doctor, as to perhaps not 50/50 but perhaps 60/40,
3 have you taken into account or attached any signifi-
4 cance to the fact that three cardiologists, that is
5 to say Drs. Rowe, Fowler and - let me be sure that
6 I have the third name correctly - and Freedom have
7 all expressed their opinions here that Justin Cook
8 died as a result of digoxin overdose?

9 A. No, I have not taken that
10 into account but I think it is certainly within the
11 realm of possibility that he died of a digoxin over-
12 dose. I would not dispute that at all. All I am
13 disputing is whether you can say it with certainty.

14 Q. I say to you they put it a
15 good deal higher than that. They regarded that as
16 being the cause of death.

17 A. With respect, I think they
18 are guilty of the post hoc ergo propter hoc fallacy
19 that I raised before lunch. I think you cannot
20 assume just because you find a digoxin concentration
21 in blood and in tissue that that is the cause of
22 death and that is the assumption they are making.

23 Q. You are more cautious than
24 they?

25 A. That is correct, on this
point.



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Q. We raised the question before lunch as to what the dose was when it was administered and whether, in light of all the information and on the assumption that there was indeed an overdose administered, whether one can make an informed judgment about whether administration was likely to have been accidental or intentional. Those are questions that I suppose reasonably arise from the findings of digoxin in this child, are they not?

A. Absolutely.

Q. Will you agree with me, Doctor, that to a considerable extent those questions or the answers to them may be interdependent. That is to say, the size of dose and the time of administration are related pharmacokinetically, are they not with the level? If you are trying to link a dose to the time of administration --

A. Yes, you have to know the size of the dose and the time of administration and the time elapsed.

Q. That is right, because each will vary as the other varies.

A. That is correct.

Q. And similarly, the size and time of the dose may have a bearing on the question



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of accidental or deliberate administration?

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A. Oh, absolutely.

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Q. You are aware of course that

5

Dr. Spielberg has given evidence here?

6

A. Certainly.

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Q. He is a member of your

8

Division at the Hospital?

9

A. That is correct.

10

Q. Dr. Spielberg told us that

11

the calculation of the dose needed to produce the

12

concentrations found in the blood and fresh tissue

13

of Cook depends essentially upon the point in the

14

distribution curve at which you assume the levels

to have occurred. Do you agree with that?

15

A. Certainly.

16

Q. If the levels occurred at the

17

very top of the alpha phase of that curve, immediately

18

after administration, those samples were recorded,

19

and if circulation stopped essentially immediately

20

upon the dose being administered, then he told us

21

that a very small dose could account for those

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blood levels and indeed he quantified it, and this

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is found at page 2147, Mr. Commissioner, of Volume

54, as perhaps as little as one-third of a pediatric

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vial.

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A. I think - maybe you should go on with your point - that does require a presumption that there was not any circulation during the resuscitation which is pretty unlikely.

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Q. And fairly, he also said, and this is found at pages 2150-2151, sir, that in light of the concentrations found in the fresh heart and lung tissues it was really implausible that that scenario be the correct one and that therefore the calculated minimum dose necessary to produce the blood level at least would not likely be the actual dose administered.

13

Would you agree with that?

14

A. Yes, I would.

15

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Q. That is really rather akin to the 5-second hypothesis we were talking about this morning, is it not?

17

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A. That is of the same general structure.

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Q. Then at the other end of the spectrum, Dr. Spielberg told us that if the serum level of 72 represented a steady state of distribution, then the dose necessary in order to have produced that as steady state would have been on the order he said of 12 adult or 120 pediatric ampules, and



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2 that is page 2151, sir, and although not necessarily
3 committing yourself to those particular numbers,
4 I take it you do not agree violently with that
5 analysis?

6 A. I don't disagree.

7 Q. You don't disagree?

8 A. No.

9 Q. He considered that extremely
10 unlikely too, and I take it you would agree?

11 A. I think it is unlikely.

12 Q. Just the administration of
13 a dose that size makes that an implausible scenario,
14 does it not?

15 A. It does.

16 Q. He considered therefore that
17 the blood and tissue concentrations in Cook probably
18 represented some point along the alpha phase
19 of the distribution curve when the drug was in the
20 central compartment or central volume of distribution
21 and he assumed, for the purpose of doing that
22 calculation a volume of distribution of 1 litre per
23 kilogram and on that basis, and taking the approximate
24 weight of this child, he calculated that a dose of
25 something less than one adult ampule could produce
the recorded levels both in fresh tissue and in serum



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that were recorded in this case?

3

A. I think that is correct.

4

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Q. That is an order of number that
you would accept, is it?

6

A. Yes.

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Q. Do you regard that as a
reasonable assumption to make with respect to the
volume of distribution to plug into the calculation?

9

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A. Yes; it is very arbitrary.
What you choose is a volume of distribution. If
you look at Dr. Kauffman's report, which I guess is
in evidence, is it?

13

14

Q. No, it is not, but it is
available.

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THE COMMISSIONER: Everybody has
it except me.

17

18

MR. LAMEK: You have touched a
sore point, Dr. MacLeod, the Commissioner does not
have it.

19

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THE WITNESS: Okay, I will lend
you my copy.

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He used the figure of 1.3 litres
per kilogram. Dr. Spielberg used 1, you say.
There is a recent paper by Dr. Hastreiter who you
will hear from I guess which comes up with a figure



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3 of 0.6 litres per kilogram, so there is a range. Of
4 course, if one assumes that there is not any
5 circulation at all, that there is sort of death
6 within seconds after administration, the volume of
7 distribution may be very small indeed, you know,
8 .05 litres per kilogram, very small.

9 Q. But on that very point,
10 Dr. Speilberg, as I understood him, agreed with me
11 that the point that one selects on the distribution
12 curve is, essentially the interval that one assumes
13 between administration and cessation of circulation,
14 for all practical purposes, really determines the
15 answer that you get out of the bottom of the
16 calculation.

17 A. That is correct.
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Q. That is to say, the closer you take the sampling time to the time of administration the smaller the figure you plug in for volume of distribution and therefore the smaller the dose that you get to produce the result?

A. The smaller the dose, theoretical dose required.

Q. Yes.

A. That is correct.

Q. And conversely the larger the volume of distribution the larger the dose that you produce as the one required to produce the levels?

A. That is correct.

Q. Now, selecting, as I say, and don't impute any inappropriate reason for it, in selecting as I say a volume of distribution of one litre per kilogram Dr. Spielberg's required dose to produce the levels came out, as I say, at something rather less than one adult ampule of digoxin. Is there not a point, Dr. MacLeod, along the alpha phase where the dose necessary to produce these levels exceeds one adult ampule?

A. Yes.

Q. Clearly. Now, Dr. Spielberg



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has suggested that one adult ampule may indeed be administered in error, of course, it is entirely possible.

A. Yes.

Q. Do you have a view as to the likelihood of digoxin having been administered in error if the dose required to produce the recorded levels is greater than one adult vial. If you are talking two or more vials ---

A. Well, I think it comes highly unlikely that an error of that sort would occur; at least, it is unlikely that that would occur when the dose was being prepared in the relative peace of the nursing station. It perhaps is feasible in the midst of an arrest but it is certainly a much, you know, several orders of magnitude less likely as a medication error.

Q. And I take it therefore that the point along the alpha phase or, in other words, the interval that you assume between administration and cessation of circulation becomes very important as to the question of accidental as opposed to deliberate administration?

A. Yes.

Q. The greater that interval



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the more remote becomes the possibility of
accidental administration, I take it. Is that fair?

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A. That is correct.

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Q. May we then in that context

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look at the question of time. Assuming continuing
circulation of blood let me ask you first is
distribution time dependent?

8

A. Yes, surely.

9

Q. It may not be a straight line

10

graph of distribution from blood to tissue but it
is a time dependent process, is it?

11

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A. Yes. Well, actually, this

13

paper that we put in and then put aside shows you
very well the kind of alpha phase that you - we

14

can use it well for this purpose because in fact

15

the lower curve there is exactly the kind of dose

16

that we are considering. Mind you, this is an

17

administration to normal volunteers who I think were

18

in their twenties or thirties.

19

Q. Yes.

20

A. So, I mean, they are not

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comparable in this sense. But the shape of the curve
is the same. This is exactly the kind of curve that
you would expect in a child as well.

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Q. All right.

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A. I should say there is one other difference here and, that is, in these cases these doses of digoxin were administered by a pump over a period I believe of one hour. So, this was not a rapid administration.

Q. Well, I have to say to you, Doctor, that the distribution curve shown there follows essentially the same pattern as those that we have seen and will be produced by an intravenous bolus injection?

A. Yes. Yes, that's as you would expect.

Q. Yes.

A. The only thing that would differ with a more rapid intravenous administration is that the actual peaks will be higher.

Q. Yes.

A. So, you start from higher up on that steep curve.

Q. Yes.

A. But with respect to your question about time dependents in this paper there is a calculation of the half time for that steep phase. It is on page 5-10 at the top of the page and that table where it says Distribution Half Life.



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Q. Yes.

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A. That's what probably was

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called a alpha half life by Dr. Spielberg and you

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can see for the three different doses there are

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different times, they have a .45 hours, .27 hours

7

or .32 hours. So, we are talking about something

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like 20 minutes.

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Q. Yes, 15 to 20 minutes, that

order.

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A. 15 to 20 minutes, yes.

11

Q. Yes. Now, given the

12

information that we have about the digoxin levels

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in the blood and in the fresh tissues of this child,

14

Justin Cook, can you tell me first, Doctor, whether

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you consider it likely the digoxin was administered

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during the resuscitation efforts here; that is to

17

say, Code 25 was called at 4:20 in the morning and

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death was pronounced at 4:56. Given the concen-

19

trations that we have, do you consider it likely

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that digoxin was administered within that period

of the complete cessation of circulation?

21

A. Can I just draw a quick

picture?

22

Q. Yes, of course.

23

A. Because I am not sure I made

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1
2 the point clearly this morning. Why I am concerned
3 about this and it is really again the lack of
4 knowledge and I am sure you are all sick of hearing
5 that we don't know, but the truth - so, you know,
6 you've got this distribution curve for digoxin and
7 here, you know, you've got an alpha half life of
8 let's say 20 minutes for the sake of argument. I
9 mean, it is logical to assume that you've got a
10 converse of this which represents the distribution
11 of the drug into heart. So that if you look at this
12 that, you know, with different concentrations, this
13 presumably represents the increase in concentration
14 in heart muscle as this concentration comes down.
15 Can you see this, it is not too much at an angle?

16 Q. Can you swing it a little,
17 not so much that the Commissioner can't see it.

18 A. Now, this is what logic would
19 tell you happens but what we don't really know and
20 the point I was trying to make before lunch, we can't,
21 it's possible that what happens is this, you know,
22 maybe it goes way up and then redistributes and
23 eventually levels up. We don't know because we
24 don't have samples at five minutes or five seconds,
25 to take an extreme example. So, we can't be sure
but obviously there is a time dependent distribution



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2 of the drug into the tissue. It is just that we
3 don't know the characteristics because we don't
4 know the shape of that curve.

5 Q. Yes.

6 A. So, I mean, having said
7 that I will say, I think my answer to your question
8 is that it is likely that it would require some
9 period of time for you to achieve a concentration
10 of 1100 plus nanograms per gram of tissue in the
heart.

11 Q. Yes.

12 A. Whether that time is 10
13 minutes or 20 minutes or half an hour, I can't say
14 with any certainty. Well, I mean I can speculate,
15 but you know, it is speculation based on nothing
16 much more than my intuition based on 15 years of
17 experience in clinical pharmacology. It is not
based on any kind of hard data.

18 Q. Well, Doctor, I don't mean
19 to flatter you but 15 years of experience in
20 clinical pharmacology gives your intuition a rather
21 better base than it gives ours.

22 A. Not much.

23 Q. Can you give us your intuition?

24 A. I imagine that the curve is
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something like the converse of the distribution curve. So that if it disappears from serum with a half life of 20 minutes then it probably appears in myocardium with a half life of 20 minutes. So, taking that assumption, it would probably take more than a half an hour to achieve this kind of concentration in myocardium. But I can't be dogmatic on it.

Q. No, I recognize that you can't. All I can ask you is for your best judgment on the thing, Dr. MacLeod.

Okay, would it be helpful to you to have the Cook chart beside you?

A. I've got it.

Q. Oh, you've got it?

A. Yes.

Q. We know from pages 27 and 29 in that chart, Doctor, if you could just turn to it, at the bottom of page 27.

A. Yes.

Q. And the nursing note, Nurse Nelles' nursing note on page 29 that this baby got into trouble at about 3:45 in the morning.

A. Yes.

Q. And Dr. Kantak was called



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about that time and he is said to have administered
Inderal, first .4 severally described as milligrams
or millilitres. Would they be the same for this
purpose?

A. I am sorry, this is
propanolol you are talking about?

Q. Yes.

A. It is 1 milligram per cc,
so, it is the same thing.

Q. First .4 millilitres and then
subsequently 2 millilitres.

A. Yes.

Q. And it appears that there
was a syringe said to contain Inderal or propanolol
taped to the baby's bed. Indeed, if you will turn
to page 13 of the chart, Doctor, you would see on
the bottom order there Dr. Kantak's order to
continue the propanolol and keep 1 millilitre, 1
millogram of propanolol by the bedside?

A. Yes.

Q. Now, the Inderal that was
administered at that time apparently had no effect,
although, it had had a good effect at 6:00 p.m.
the previous evening when the baby had a blue spell
at that time too and the evidence appears to be,



(Lamek)

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Doctor, as you may well be aware is that the Inderal in that syringe had been obtained earlier from another ward. Is that your understanding of what had happened?

A. I have been told that. I don't know the basis for that. I am sorry, I am curious about your statement that the Inderal didn't have any benefit. It says with good response but I guess that maybe refers to the response to atropine.

Q. Yes, that means to the atropine, Doctor.

A. Yes.

Q. Because if you look on page 29, the nursing note, the middle of the note:

"On his arrival propanolol was administered, baby remained markedly cyanosed, another dose of propanolol was administered and doesn't seem to have had any effect."

A. No.

Q. Now, at 6 o'clock the previous evening it had worked like magic on him and got him out of the blue spell right away.

A. Yes, okay.

Q. Now, as far as the origin



11 1
2 of that Inderal is concerned, as I say, the
3 indications are that it was obtained from another
4 ward earlier in the day and taped to the bed
5 pursuant to the orders of Dr. Kantak that we have
6 just looked at. There is no suggestion that I
7 am aware of that it was obtained at a time when there
8 was frenzy or excitement or chaos or anything of
9 that sort.

10 Now, Doctor, recognizing that the
11 strangest errors can occur, in your opinion is it
12 likely that an ampule of digoxin would be mistaken
13 for an ampule of Inderal especially if there were
14 not unusual stress present in the situation?

15 A. No, I think that is an
16 unlikely medication error.

17 Q. Now, we also know that
18 atropine was administered at about shortly after
19 Dr. Kantak's arrival. Indeed, if you were to turn
20 to page 30, although that is a list of the drugs
21 administered on the arrest it also lists the
22 medications administered immediately prior to the
23 arrest. We have just referred to the Inderal .4
24 and .2 millilitres. There was then at 4 o'clock an
25 administration of .06 millilitres of atropine,
.1 milligrams.



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Again, Doctor, you are familiar with the appearance of ampules of atropine and of digoxin. Is it in your view likely that there would be confusion between those two ampules?

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A. There is more possibility certainly than with Inderal, at least, the ampules are the same colour or colourless, I should say.

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Q. Yes. On the other hand, if we were to look at page 29, as you have pointed out, the atropine appears to have produced a good response?

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A. Yes.

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Q. What is the response that is hoped for with atropine?

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A. Well, they are looking for an acceleration of the heart rate there.

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Q. And that is not likely to have occurred I take it had digoxin been administered in mistake for atropine?

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A. No, there probably wouldn't have been any change in the heart rate with digoxin.

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Q. Is it therefore reasonable to infer that what was administered as atropine in light of the noted response was indeed atropine?

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A. I think that is a reasonable assumption.



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Q. Now, it is also clear from page 30, Dr. MacLeod, that at 4:05 morphine was administered, and it is not clear from the chart why it was administered and I don't know whether you have any thoughts on that.

A. No. I actually don't know why it was administered; perhaps as a treatment of heart failure which was progressive.

Q. The child was regarded as being very irritable, as I understand it, and it might have been for that?

A. Sometimes it is used to reduce agitation.

Q. Yes. And I tell you, Doctor, upon my review of the chart I have not found any other order for the administration of morphine or any other indication of its being a PRN administration.

A. Yes.

Q. But I am also able to tell you from the report of Dr. Cimbura from the Centre of Forensic Sciences that morphine was found in his blood on the drug screen that was performed at the Centre. I ask you on that basis, is it fair to infer that morphine was in fact given as it was apparently intended to be given?



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A. I think that is a reasonable inference.

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A. Which was 4:56.

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Q. 4:56.

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A. Yes, I think it is likely that it fell within that time interval.

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Q. That it did fall within that time period. In that case, I am a little puzzled because I want to know from you, please, for which drug it was mistaken~~only~~ administered.

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A. Wait, you are changing horses here.

Q. No, I thought I said is it likely that it was mistaken. I think I asked you



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MacLeod, dr.ex.
(Lamek)

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whether it was likely that it was mistakenly

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administered in the period between 3:45 ---

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A. Oh, I am sorry. You know,

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it is likely that it was administered, whether it

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was mistakingly or in some other fashion.

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Q. Yes.

A. I note one thing you said
in your long question there --

Q. Yes, I'm sorry, they are
long.

A. You said, rather longer
than 30 minutes. You know, I would say that 30
minutes is a reasonable time; that is probably a
minimum time in my best judgment, but it doesn't
necessarily have to be very much longer.

THE COMMISSIONER: 30 minutes
before the arrest, did you say, before the
pronouncement --

THE WITNESS: Between the time of
the administration of digoxin and the ultimate
demise.

MR. LAMEK: Q. Yes. You are
talking about 30 minutes.

A. Yes.

THE COMMISSIONER: I am sure that
is what you mean. I am a little confused because
the child was -- the arrest was at 4:20, and I take
it you are assuming that there is some kind of circula-
tion going on. There isn't always, though, is there,
circulation going on?



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THE WITNESS: No. It may not be normal, sir. It is unlikely to be normal, but if the cardiopulmonary resuscitation has been carried out in an appropriate fashion, there is certainly some circulation.

THE COMMISSIONER: There will be some circulation even though that child will never really start to have normal circulation again?

THE WITNESS: So, I mean, that might lengthen the time estimate. That is certainly another variable that has to be considered. When I say 30 minutes, which is really a best guess, I am talking about the time between the time required for digoxin to reach a concentration of 1100 plus nanograms per gram of tissue after administration.

THE COMMISSIONER: That is before the circulation stopped; which may or may not be the time that the child was pronounced dead?

THE WITNESS: That is correct.

In this child it is pretty difficult to know how much circulation there was during that resuscitation procedure.

THE COMMISSIONER: They would not pronounce the child dead as long as there was some circulation?



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THE WITNESS: Well, the circulation that there is is mechanical. I mean, it is circulation being maintained by pumping on the chest, you know. So there is certainly circulation, and we know that because people survive after rather long cardiopulmonary resuscitation, and the whole point is to keep enough blood circulating to keep the nervous system alive.

MR. LAMEK: Q. Can we just work back on it, doctor, now that I understand it clearly.

At 4:56 the resuscitation effort ceases and the child is pronounced dead. Now such circulation as there had been up to that moment, if indeed there was any up to that moment, may have been partly spontaneous on the part of the child or may have been mechanically induced by cardiopulmonary massage?

A. That is correct.

Q. And to the extent, I take it, that circulation is impaired, is it reasonable to infer that distribution may be slowed?

A. I mean, there is no doubt that this must alter the pattern of distribution.

Q. Yes.

A. Again, we don't know how,



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precisely, but it would certainly be in the direction
of slowing it, as you say.

Q. And if I understood you,
I take it working back from 4:56, which is the
last possible time in which there could have been
circulation, spontaneous or mechanically induced,
your better judgment is that the dose was probabaly
administered more than 30 minutes before that moment?

A. That is correct.

THE COMMISSIONER: Before that?

MR. LAMEK: Before 4:56.

THE WITNESS: Prior to 4:26 is
what we are really saying.

MR. LAMEK: Q. Prior to 4:26.

A. 30 minutes before 4:56.

Q. The better judgment is
that the dose was probably administered prior to 4:26.

We have looked at the drugs that
were ordered and apparently administered between 3:45
and I believe 4:26, and there was Bicarb. only in
the meantime. The only other drug we have not yet
looked at that was administered between 3:45 and 4:26
was Bicarb. at 4:23.

Is it likely there was confusion
there, doctor?



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A. I would think not. It is a rather large ampoule and pretty hard to confuse.

Q. So of all the recorded drug administrations between 3:45 and the absolute cessation of circulation at 4:56 - and I take it that either they were too late to fit your best judgment of the timing or the possibility of error is unlikely, in your view?

A. Yes. Although I think you have to grade the degree of unlikelihood, if you will.

Q. I understand.

A. I would think, for atropin, morphine, probably very unlikely; for the propranolol that was in the syringe on the bed, I don't know.

Q. That is possible?

A. It depends very much on the circumstances under which that was drawn up and where it was drawn up. But, altogether, I think it is unlikely for all three of them.

Q. Does that then take us to one of two possibilities, doctor; that is, either that digoxin was administered prior to 3:45 - perhaps again accidentally, and we may have to explore the possible occasion - or after 3:45 but perhaps not



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accidental? Are those the options to which we are driven?

A. Yes. Well, I am sorry, can we take them one at a time?

Q. Yes.

A. Prior to 3:45?

Q. Prior to 3:45 is one possible time for the administration of digoxin?

A. Yes.

Q. Now, do you regard that as likely? Do you, as a pharmacologist, regard that as likely?

A. No, I find that very unlikely, because you are getting too far out on this alpha distribution phase; so then you are into the multiple vial and large volumes, or relatively large volumes. I find that unlikely.

Q. Do I therefore understand you that your likely timeframe for the administration of the drug is between 3:45 and 4:25?

A. Yes, that is correct.

Q. And of the drugs known to have been administered in that period, that 35-minute period, 40-minute period --

A. 40-minute period.



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CC7 2 Q. -- 40-minute period, I have
3 asked you as to your assessment of the likelihood
4 of error, and you have told me, obviously, it is not
5 uniform, the possibility with respect to the inderal
6 taped to the bed; in your view, a lesser likelihood
7 with respect to the atropin and morphine.

8 Do I have it correctly now?

9 A. Yes, that is correct.

10 Q. Does it therefore come to
11 this; that unless an error occurred with respect
12 to the inderol taped to the bed, one has to look for
13 something other than a drug error for this admini-
14 stration?

15 A. I think that is correct.

16 Q. And just to look at the
17 other possibility; that is, prior administration,
18 prior to 3:45, even though you do not regard that
19 as likely, doctor, I tell you the only other recorded
20 drug administration I can find in the chart was
21 propranolol at midnight, and I take it that would be
22 much too distant in time for you to accept as a
23 likely time of dosage?

24 A. For a medication error?

25 Q. For a medication error to
produce these levels in this child at five o'clock
in the morning.



CC8

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A. Yes, I agree.

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Q. And just let me be clear

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with respect to the inderal taped to the bed. I

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recognize that you cannot have any absolute assurance

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with respect to that. Did I understand you to say

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that you would have thought that was an unlikely
error?

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A. Well, I said that because

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of the colour of the ampoules.

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Q. Yes.

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A. I mean, nothing is certain

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when it comes to medication errors, as you have

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heard I guess already. To me you know to make

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a mistake on propranolol versus digoxin or versus

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adult strength digoxin, you really have to make a

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double error; you have the wrong colour ampoule -

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and maybe it is a triple error; you have the wrong

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colour ampoule, the wrong name on the ampoule and it

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is the wrong volume in the ampoule. So, you are

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dealing with a 2 ml ampoule versus a 1 ml ampoule.

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You have also got an order there that says very
specifically, let's have 1 ml strapped, taped to
the bed.

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Q. Yes.

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A. 1 ml of propranolol solution

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containing 1 mg. of propranolol. You get to a point where there are too many errors required and it strains credulity.

Q. Doctor, I recognize the reservation that you have about whether digoxin intoxication was the cause of this child's death. Let us leave that to one side for the moment.

In the light of all that you know about the sequence of events leading to this child's death and all that you know about the levels of digoxin recorded in his body, blood and tissues, do you have an opinion as to the likelihood that the dosage of digoxin which this child received, whether it caused his death or not, the likelihood as to whether that dose was accidentally or deliberately administered?

A. Yes.

Q. What is it?

A. I imagine that it was a deliberate overdose.

Q. Can we look then at the case of Allana Miller.

Now, sir, is there anything else that you would like to say about Cook?

A. No, I don't think so. Well



CC10

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I think that it should be - I'm sure you have been over the question of lidocaine concentration in the blood.

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Q. Yes.

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A. That is an indicator of the occurrence of medication errors, particularly under the stress of cardiac resuscitation, and I think that clearly indicates - maybe it wasn't a medication error; it may just be a charting error and somebody forgets to write it down. I have very little difficulty with that because I think lidocaine is a drug very commonly used in the resuscitation procedure and there are very few resuscitations, in my experience, where lidocaine isn't used.

15

Q. Certainly, lidocaine --

16

17

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A. So, it doesn't necessarily represent a medication error, although it comes through in the Forensic Science Report as being an unexpected drug.

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Q. And certainly, and fairly, it is something that was apparently administered and not recorded?

22

A. Yes.

23

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Q. And one can't discount entirely the fact that that occurred.



CC11

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Do you have the Miller chart?

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A. No, I don't have it.

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Q. I think the Registrar will

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provide it to you if you should need it.

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Now, with respect to Allana Miller,

7

Dr. MacLeod, as you know, levels of 78 nanograms

8

per ml. were recorded by the Hospital's lab and

9

69 nanograms by the Centre for Forensic Sciences in

10

post mortem blood samples for this child. She had

11

an ante mortem level measured on March 19th of 0.6

12

nanograms and there were lower levels in fixed heart
and lung tissues.

13

Again I start with the question,

14

as I started with Cook, is it likely in your

15

opinion, that the post mortem blood levels indicate

16

the child received an unprescribed dose of digoxin?

17

A. Yes.

18

Q. And I take it, once again,

19

you would have the same difficulty in opining whether

the death was caused by digoxin intoxication?

20

A. Yes. The case I am

21

familiar with, it doesn't have anything that could

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be said to be absolutely diagnostic for digitalis

poisoning as a cause of death.

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Q. Do you regard it as

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probable that death was caused by digoxin intoxication?

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A. I think -- would you
excuse me just a moment?

Q. Yes, of course.

A. May I just find the
proper place in the chart here.

I think it may be a little more
likely than in the case of Cook in that this child
was not, as far as I can see, as likely to be prone
to Sudden Death as was Cook.

Q. Now Dr. Spielberg has
suggested with respect to this child, as possible
explanations for the serum levels that were measured
in her post mortem blood, the possibility of
resuscitation trauma and certainly there is
evidence in the autopsy report of fairly extensive
damage to chest and organs in the course of
resuscitation.

A. Yes.

Q. Which he says may have
caused elevations in the blood level, which I
understand to be saying essentially that the
recorded post mortem levels are, to some extent,
artefacts.

I ask your view on that suggestion
as an explanation for the elevated levels.



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CC13 2 A. I think that is within the
3 realm of possibility. I find it difficult to assess
4 the likelihood of that happening. Certainly, if it
5 has happened, it is an increase of greater degree
6 than we have seen in other cases, but it is within
7 the realm of possibility.

8 Q. Now once again, I guess
9 we are into the question of how much digoxin and
10 when it was administered in order to produce those
11 levels.

12 Could we look first at the time
13 element of that please, doctor.

14 At page 42 of the chart there is
15 a note written by Nurse Nelles, the lower half of
16 the page, the period beginning at 7:00 p.m. on
17 March 20th and three o'clock on the 21st. The
18 child, even at the beginning of that period, seemed
19 to have had a rather slow heart rate ranging from
20 73 to 59 and irregular. But further down the note
21 approximately 1:45, the heart rate was noted to be
22 54 and very irregular.

23 The child was stimulated and the
24 apex came up to the 70s; it happened three to four
25 times. Then the child began to gag and vomit, large
amounts of very thick, clear mucus, suctioned; further



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TORONTO, ONTARIO

MacLeod
dr.ex. (Lamek)

4203

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CC14 2 amounts of mucus. Then lasix was administered by
3 IV push. Seizure activity at 2:45, seizure activity;
4 no heart rate heard; CPR started; Code 25 was
5 called.
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Resuscitation efforts are to no avail and the baby was pronounced dead at 3:27.

I take it heart rate from 73 down to 59, the rate recorded at the start of that period, is slow heart rate for an infant?

A. Very much so.

Q. At 1:45 it drops even lower, it goes down to 54. There is some stimulation. It gets up to 70, drops back again three or four times, we are told.

Then there is vomiting; then there is some seizure activity and then there is an arrest.

Does that sequence of events, Doctor, from 1:45, suggest digoxin toxicity?

A. Not particularly to me.

Q. You have a slowing heart rate and increased irregularity, vomiting and some seizure activity?

A. I think it is certainly compatible with - there is nothing there though that could be said to cry out this is digoxin toxicity.

Q. Is that because it is not so startling a departure from what has preceded it?

A. There really - it looks like a gradual process in fact and bradycardia in fact is



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not unusual, slowing of heart rate is not unusual in infants as a mode of cardiac death, in my understanding.

The question of vomiting, vomiting stimulates vagal nerve activity and tends to slow heart rate further and might in fact even be a precipitating factor I suppose in the arrest. So there is nothing here that seems strikingly unusual.

Q. It is recorded that Dr. Soulioti administered Lasix at about 2:40.

A. Yes.

Q. Administered Lasix by - what is that - 6 milligrams?

A. 6 milligrams.

Q. By IV push at 2:40 and it occurred to Dr. Spielberg to put together two related thoughts on this, and I do not know whether you are aware of what he said. First he noted that five minutes before the arrest, at 2:40, this baby received an IV dose of Lasix and he raised the possibility, this is found, Mr. Commissioner, at Volume 55, page 2222, he raised the possibility that what was thought and intended to be Lasix may in fact have been an ampule of digoxin. That is to say, he raised the possibility of drug error on that administration. I was looking at an ampule of Lasix this morning,



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furosemide, and showing it to Dr. Bain and that is
the dark brown one, is it not?

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A. That is correct.

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Q. And once again, Doctor,
recognizing the possibility that anything can happen,
do you consider it likely that confusion would occur
between ampules of digoxin and Lasix?

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A. I think you have to qualify it
as you have that anything can happen and in fact
does happen, is shown to happen, but one would not
a priori expect somebody to mix up furosemide and
digoxin, particularly on a cardiac ward where they
probably would be familiar with the colour of the
digoxin ampule.

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Q. And indeed of the furosemide
ampule?

A. Indeed probably of the
furosemide too, although not necessarily.

Q. Although many of these children
are in fact on Lasix, according to the charts.

A. I appreciate that.

Q. Dr. Spielberg's second point
as I understood him, was this, that if in fact dig.
were given by IV push in error instead of Lasix, and
if it were administered rapidly, as apparently the



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Lasix was, it could have acted very quickly to kill the child, not by digoxin but by propylene glycol which he says makes up 40 per cent of the contents of the parenteral digoxin preparation. Do you have any comment on that proposition?

A. I think it again is within the realm of possibility. I am just looking to check exactly on Miller's - do you know offhand Miller's weight?

Q. I can tell you.

A. She was 11 months old, at any rate.

Q. No, weight at birth - I don't know what her weight was.

A. It should be marked on here. Her weight was about 6-1/2 kilos, so I think that even assuming that digoxin was given instead of furosemide in error, you are talking about a dose of 6 milligrams of furosemide which is about one-third of an ampule, you would have to relate that to one-third of an ampule of dig., assuming that one error does not automatically lead to another so you draw up the same amount. So we are really not talking about very much propylene glycol to a 15-pound child. In my view it would be unlikely that that amount of propylene



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glycol would cause a sudden cardiac arrest. I fully appreciate that there are a number of cases, reports of sudden death after intravenous administration of drugs that require propylene glycol as a diluent. There also are many, many more people who receive these drugs by rapid push and have no adverse effect from propylene glycol at all. So what we are talking about is a relatively rare adverse reaction in some patients, since most of the literature in fact deals with adults, to propylene glycol, so it is possible, certainly. I think it is a scenario that should be considered.

Q. Let me be fair and let me be clear, we are adding possibility to possibility in this case, are we? It is possible that digoxin was administered by mistake for Lasix and it is possible that if it was the propylene glycol content in the preparation could have acted very quickly to produce death in the child?

A. Yes. I would suggest to you that it is also possible that the vomiting was associated with vagal stimulation which caused cardiac arrest. That is equally possible and probably more likely on balance than the other.

Q. Doctor, are you able to help us



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with your best judgment as to the dose and the time of administration to produce the levels that were recorded in this child? I invite you of course to make such a discount as you will for the multiplier effect in post mortem blood.

A. Do you have the sheet from the Forensic Sciences Centre?

Q. Yes, I do.

A. I don't actually recall offhand the hours elapsed after death before those samples were done. Is that information there?

Q. I think they were taken at autopsy and then appear from - it should be in the autopsy report, Doctor.

MR. OLAI: Page 52.

MR. LAMEK: Q. Page 52, thank you.

A. 52 of the chart?

Q. Of the chart, yes. Hours after death, six.

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A. I think you have the same
quandary that you have with Cook. You have the
multiplier issue, which means that this level might
have been really quite substantially lower than it
appears on this measurement, but you also have the
difficulty of not knowing the time of administration,
the time elapsed between administration and death.
So you, in other words, just don't know where you
are on that alpha distribution curve. So, anything
I say is just speculation. It is not really even
legitimate to speculate in this case.

Q. I take it, in this case,
the administration shortly before the termination
of circulation is not out of the question because we
have no idea what the tissue concentrations were?

A. We do have tissue measure-
ments --

Q. The fixed tissue, though.

A. Oh, the fixed tissue, certainly -
subject to some skepticism, I suppose.

Q. Yes. And this, after all,
was a child who had been on digoxin or had received
digoxin?

A. Yes, that is correct. So,
your point is well taken. It is quite possible
that the administration was at, say, 2:40.



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Q. It is possible?

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A. Quite high up on the

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alpha distribution phase, thus not requiring a large
volume of distribution.

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Q. If, in fact, the level,

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suitably discounted to give effect to the multi-
plier, were a steady state distribution, could
you give us some idea of the time of dosage and size
of dosage necessary to produce it? That, I take
it, would be a very large dose?

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A. It would certainly be a

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larger dose. I'm not sure -- say you accepted a
post mortem multiplier of 4, which would be in line
with our recent experience at the Hospital --

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Q. Looking at 17 or 18?

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A. -- so you're talking about

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a steady state concentration of maybe 18 or 19 --

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Q. Yes.

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A. -- certainly, that would

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require a dosage in excess of therapeutic, but it
would not require multiple vials of administration on
a daily basis or something like this.

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Q. And that is the extreme

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high end of the dosage, I take it, doctor, assuming
steady state distribution?

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A. Yes. It is very difficult --

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I think it would probably be erroneous to assume
steady state distribution or concentrations for --

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Q. For any parameter.

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A. Although that assumption
has been made in the past in some of the preliminary
testimony.

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Q. Yes.

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A. It is not completely out
of the question. I am not sure you want to get into
that but, clearly, there are very long-term survivors
after major overdoses of digoxin. So, I certainly
would not want to dismiss the idea as ridiculous that
you could get out for four, five, six, ten hours
beyond the administration. That is why it is
really very difficult to pin down time.

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Q. In terms of likelihood,
I take it that the greater the distance you posit,
the less the likelihood; is that fair?

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A. There presumably is a lot
of variation between individuals and their ability to
tolerate the insult of a digoxin overdose. There are
cases in the literature of people having levels of
200 nanograms per ml. and surviving for two hours;
there are cases of people having levels of 20 nanograms



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per ml. and surviving for 10, 12 -- surviving, period,
without treatment.

So, I don't know what the likelihood
is. And you have to add to that the fact that
children generally are relatively more resistant to
digoxin poisoning than are adults. So, if anything,
they are better able to withstand that, although,
in these infants, you have --

Q. You have got sickness --

A. You have another problem
because you have --

Q. -- and heart disease.

A. You have heart anomalies
and disordered circulation that may predispose them
to --

Q. Doctor, in light of the
inability to either fix upon a dose size or the
time of administration with any confidence at all
because I understand that is what you were
saying --

A. That is really what I'm
saying.

Q. -- do I take it that you
cannot form any judgment as to the likelihood of
accidental or intentional administration?



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A. I would find that very hard to do in this case.

MR. LAMEK: Mr. Commissioner, I have taken it, since you have to leave at ten to four, that we will go straight through?

THE COMMISSIONER: Yes, I think so.

MR. LAMEK: Q. Can we then look at Kristin Inwood, Dr. MacLeod.

Once again, unless there is something else you want to say about Miller. I did not mean to cut you off.

A. No. I have really nothing to add, I think, to what has been said to you before.

She may, in fact, illustrate some of the artefact that results from agonal events. I think there is greater likelihood in this case than in others.

Q. Because of the reported damage at autopsy?

A. Yes.

Q. As far as Kristin Inwood is concerned, Dr. MacLeod, I take it the matter of prime concern is the level of 491 nanograms measured in post mortem, I gather serum, at the Centre of Forensic Sciences? Is that the major matter of



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concern?

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A. I assume that is the major

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matter of concern for this hearing, anyway.

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Q. Is it a major matter of

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concern for you, as a clinical pharmacologist?

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A. I must say that this case,

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more than any other, made us re-examine some of our
presuppositions about the other cases. This is a

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case that we were really unaware of until the

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preliminary hearing, as you probably have heard.

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Q. Yes.

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A. When we were confronted

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with the level of 491 nanograms per ml., we really

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could not think of any -- it was unthinkable that

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that could be a steady state of concentrations.

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Q. Yes.

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A. Because it would require,

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as I am sure you have been told, just massive doses
of administration. So, it forced us back up the

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alpha distribution curve there and forced us to

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really consider the possibility that digoxin might

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have been administered, in a case like this, right

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at the moment of death, or very close to it. I

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think that actually led to a lot of the other

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pharmacokinetic calculations that you have heard from

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Dr. Spielberg.

BmB.jc
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Q. Well, can we look first at the nature of the sample and I don't know how fully you are informed of the evidence that we have heard recently about it, it now appears that this sample was the remnant of a sample drawn at autopsy for virological examination and was probably serum not whole blood. It appears the virologists had done their thing with this sample and this was merely a remnant of it. I understand they work in serum rather than in whole blood?

A. Yes, usually.

Q. Yes. We know that the sample was apparently drawn at autopsy by Dr. Taylor and he has told us that his usual procedure in taking samples at autopsy is to draw samples from the inferior vena cava.

Finally, we know that it sat for months in the refrigerator in the Virology lab and indeed at some point it appears to have been heated, although, to what point I am not exactly sure but indeed the sample had a checkered history before it arrived at the Centre of Forensic Sciences.

I have to ask you first whether you have concern about the validity of the assay result in light of the sample's history?



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A. Well, I think one would want to know more about, you know, the effect of these conditions on the sample and one would certainly like to know very specifically whether or not digoxin was actually present in the sample. I mean, for instance, this would be an ideal sample on which to use mass spectrometry or some very specific measurement technique.

Q. Yes, I don't believe mass spectrometry was used on this. Let me just find the way in which Mr. Cimbura reported on it and I can tell you whether HPLC and RIA were used; I believe they were but let me just be sure.

MR. OLAH: Exhibit 95C.

MR. LAMEK: "C" is it, thank you.

Q. Yes, from the form of the report and Mr. Cimbura's evidence it appears the sample was assayed first by RIA then HPLC and then RIA. So, he is reporting 491 nanograms per millilitre as digoxin upon that analytical method?

A. Yes. Well, I would strongly suggest that this calls for more specific - I mean, I think it is very critical in this case to know that that is absolutely digoxin and not some confounding factor and if there is a sample it really should have



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been or should be now analyzed by mass spec.

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Q. Yes. Well, if the reading however is a reliable one, Doctor, what Dr. Fowler here referred to as a sort of a true bill and discounting, as you consider appropriate for the post mortem multiplier and so on, do you have an opinion as to whether one can infer from whatever calculated down level you choose that the level resulted from an unprescribed administration of digoxin?

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A. Yes, my understanding that this child was not on digoxin.

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Q. I don't think that to be so. She was on digoxin?

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MS. CRONK: Yes.

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MR. LAMEK: Q. No, digoxin was prescribed.

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A. She was prescribed digoxin, I'm sorry.

Q. Yes.

A. But you could certainly infer that there was some kind of an excessive dose of digoxin given.

Q. Yes.

A. And even perhaps reducing that



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figure to a tenth it still leaves you with a relatively high concentration that would be difficult to explain in any other way.

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Q. And recognizing once again the changing time/dose relationship that we have talked about, are you able to form any opinion at all as to the kind of dose, at what point in time it might have been necessary to produce the level that we have here?

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A. Well, if the level is 491 then I think that you can infer quite definitely that it has to be a near agonal event, the administration.

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Q. There could have been very little distribution after administration is what you are saying?

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A. Yes. If in fact though the level is really 49 that there is a tenfold multiplier through artefacts, whatever, or just through the normal post mortem change, then you are in a more difficult situation, you are back to something comparable to Cook and Miller where you really are just guessing.

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Q. Well, let me understand. Other than by a process of evaporation I don't suggest that is impossible, but other than a process of evaporation



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if this was serum, once the blood is drawn and reduced to serum I take it there is not going to be any multiplier effect from that point on, is there?

A. No, I wouldn't think so unless there is some breakdown, you know, something in the serum which has been broken down, say, by this heating and cooling sitting in the refrigerator for nine months that has produced some interference substance and this is why I say you need a very specific assay of that.

Q. Or had there been some evaporation then presumably the concentration would be higher in whatever liquid remained?

A. But you wouldn't expect much in the way of evaporation, I don't think.

Q. Okay.

A. Well, it depends on the refrigerator and how it was stored of course.

Q. Yes. I take it your better judgment with respect to this is that administration was probably close to the end of circulation, very close to the point of death?

A. I think so, although, again, if the level is really 49 or 100 instead of 491 then, you know, you are really back in the same ball park



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as you were with Miller and Cook.

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Q. If the level is indeed 100,
let's apply it fourfold, or fivefold, talk about one
hundred or a hundred and a quarter.

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A. Yes.
Q. And let's assume administration
very close within a matter of a very few minutes to
the time of death, are you able to give me any idea
of the kind of dose that would be required to produce
a level of 100, 125 in this child?

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A. Well, I mean, you can explain
it with almost any dose if you take it far enough back
on the alpha curve. If you take the volume of
distribution as being .04 litres per kilogram and
this child's body weight is about 3 kilos, is it,
2.7 kilos, anybody know? You people have been
listening for six months to this.

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Q. We haven't been looking at all
these weights all this time.

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A. 2.5 kilos. So, we are talking
.04. Maybe I can do the mathematics here. You are
talking about .04 litres per kilo and you've got .5
kilos, so, what have we got? You've got .1 litres.
So, you are talking about 100 mls and you are talking
about 491 nanograms per ml, so, you're talking about



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491 or 49.1 micrograms.

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Q. Yes.

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A. I guess. I hope I haven't misplaced the decimal point there by doing it quickly but you are talking about a paediatric ampule if you are taking it right back at the very top of this alpha distribution phase.

Q. Yes.

A. Because the further down you come the more you require it. So, I think you can assume almost any dose you want as being adequate to produce that. Probably not a normal therapeutic dose but a dose within one paediatric ampule.

Q. I take it even further down the alpha phase it is well within one adult ampule?

A. Oh, yes, certainly. I mean, any child this size you can really come quite a way down the alpha distribution phase and still account for it with one adult ampule, yes.

Q. Yes, okay.

A. I think if you get up to that size of a dose you can probably come down to an hour before administration, an hour before and still account for it.

Q. Yes. But in summary with respect



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to Kristin Inwood, as I understand you, Dr. MacLeod,
your judgment probably tells you that the administration
was higher up rather than lower down the alpha curve
but you cannot say with any confidence exactly where
or exactly what size dose. Is that fair?

A. That is fair, but where it
really depends is entirely on the credibility of this
491.

Q. Yes, sure. That is all even
assuming the credibility of 491?

A. Yes, yes.

Q. Yes.

A. I think the 491 can be taken
as evidence assuming that it is a specific assay that
there was an excessive dose of digoxin. I don't think
you can go very much further than that. Now, I believe
there were tissue concentrations as well on Inwood
that were very well, is that not correct?

Q. Yes. They were fixed though
I'm afraid.

A. But they were almost negligible,
is that not correct?

Q. Let me just find it for you.

MR. OLAH: Page 7.

MR. LAMEK: Thank you. Well, no,



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these were not the negligible ones. Fixed tissue, digoxin in the left ventricle 230 nanograms.

A. It is Miller that had the negligible.

Q. Yes, 79 in the left atrium, 300 in the septum.

A. Yes.

Q. And those are digoxin by HPLC plus RIA.

A. Yes. No, I am sorry, it is Estrella, Estrella is the one where it was negligible, yes. No, I think those levels are compatible with reasonable therapeutic doses and about what you would expect and they really don't help you at all with this agonal situation.

Q. It may be that all we can say of the levels in the fixed tissue is we certainly can't say they are incompatible with anything?

A. No, that is correct.

MR. LAMEK: Mr. Commissioner, I am about to move to another child and it is Pacsai and it may take a little while. Is this a sensible time to break?

THE COMMISSIONER: Yes, we will rise then until 10 o'clock tomorrow morning.



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MR. LAMEK: Thank you.

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--- Whereupon the Hearing adjourned at 3:45 p.m.
until Thursday, November 10th, 1983 at
10:00 a.m.

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FILE	PAGF	PAGT	SUB1	SUB2	SUB3	NAME	EV
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63	4126	4127	DIG LV UP	POTASS UP	EVID PRELIM	MCLE	E
	4127	0	POTASS UP	DIG UP SOME	EVID PRELIM	MCLE	E
		4128	DIG LV UP	POTASS UP	AGREE STILL	MCLE	E
	4128	0	POTASS DOWN	DIG RISE	MAYBE SIGNIF?	MCLE	E
			POTASS UP	DIG RISE?	YES	MCLE	E
			POTASS UP	DIG UP - WHICH	IS CAUSE? UNKWN	MCLE	E
	4129	0	PACS DIG LV	CAUSE POTASS?	UNKNOWN	MCLE	E
			PACS POTASS LV	CAUSE DIG?	UNKNOWN	MCLE	E
64	4238	4240	PACS DIG LV	CAUSE	HIGH POTASS SPIE	MCLE	E
			PACS DIG LV	CAUSE	HIGH POTASS POS MCLE	MCLE	E
	4241	0	PACS DIG LV	CAUSE POTASS?	25% CHANCE	MCLE	E
	4257	0	PACS POTASS	HIGH - DIG	COULD CAUSE	MCLE	E
		4258	DIG TOXICITY	POTASS HIGH	BENEFICIAL	MCLE	E
	4293	0	PACS POTASS LV	MCM	*5.6 - *5.8	MCLE	C
			POTASS LV	NORMAL	*3.5 - *5.5? YES	MCLE	C
	4294	0	PACS POTASS LV	MCM	SLIGHTLY HIGH	MCLE	C
		4295	PACS POTASS LV	ARRIVD HSC	*3.9 NORMAL	MCLE	C
	4295	0	PACS POTASS LV	< 12 HRS	*7.7 SURPRISING	MCLE	C
	4296	0	PACS POTASS LV	RISE CAUSE	DOSE POTASS?	MCLE	C
	4297	0	PACS POTASS LV	RISE CAUSE	DOSE DIG?	MCLE	C
	4311	0	DIG EFFECT	ADREN GLAND	POTASS GOES UP	MCLE	C

